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Venereal Disease Information

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UNITED STATES PUBLIC HEALTH SERVICE

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Venereal Disease Contact-Tracing in Camden, New Jersey

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THE APPLICATION of epidemiologic principles to the control of venereal disease has been made one of the cardinal points in the present national campaign against syphilis. This is a familiar concept to public health officials in New Jersey. As early as 1922, venereal disease contact-tracing was inaugurated as part of the program of the bureau of venereal disease control of the New Jersey State Department of Health (1). In the next 2 years six cities (Newark, Jersey City, Elizabeth, Trenton, Plainfield, and the Oranges) assumed the responsibility of epidemiologic control as a part of their local health department activities, each employing a nurse for venereal disease case-finding and case-holding work. In each of these cities the work has been carried on continuously ever since its inception. The State program also has been continued although less intensively than in the cities during this entire period of time.

LEGAL BASIS FOR CONTACT-TRACING

The development of a venereal disease contact-tracing program has legal sanction in New Jersey. One of the laws (2) enacted in the war-time fervor of 1917 and 1918 made it the duty of physicians to report to the State department of health by name and address all cases of venereal diseases treated by them and to include in the report the name of the probable source of infec-

tion. The control law (3), enacted a few months later, admonishes local health authorities to use "all reasonable means" to ascertain the existence of cases of infectious venereal diseases in their respective jurisdictions.

The attempt to get from newly reported cases information about contacts and to require these suspected persons to submit to examination has been considered in New Jersey as "reasonable means" of finding infected persons.

Where infected persons are being treated in a group, as in the clinic, an opportunity to do intensive epidemiologic work exists. Obviously, the time that the treating physician in a busy clinic can give to each patient is limited. Hence, the State department of health has encouraged local health departments, whenever the size of their clinics warrants it, to employ a specially trained person to interview patients and to follow up all suspected cases.

An indication of how successful a trained person can be in securing information from infected persons came from one of the New Jersey clinics as early as 1924. In this instance the medical case worker of the clinic at the Orange Memorial Hospital obtained the name of the source of infection from 21 of 32 infectious venereal disease patients (4).

Ever since the enactment of these laws it has also been the practice of the State department of health to refer immediately to the local health officer concerned any information about the sources of in-

From the New Jersey State Department of Health.

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fection given by private physicians reporting cases of venereal disease under their care. This has been interpreted as sufficient cause for local health officers to have such persons examined. The names of the reporting physician and patient are carefully guarded by the State department of health as confidential information.

A study of the effectiveness of this program in New Jersey, as carried on through the cooperation of private physicians and State and local health departments, was made in 1937 after the more intensive work in some of the clinics was begun by Norman R. Ingraham, Jr., M. D., and reported in *Venereal Disease Information* (5).

THE EPIDEMIOLOGIC PROGRAM IS STRENGTHENED

Through Federal funds allotted to the States under Title VI of the Social Security Act, the New Jersey State Department of Health has been able within the past 3 years to employ several case workers to strengthen the epidemiologic program already generally accepted in this State. These workers have been assigned to communities where little or no contact-tracing had been done previously and where the local health officers expressed a desire for demonstration of its value in public health programs.

One of these demonstrations is reported here as another indication of the value of contact-tracing in the public health program of a community. No claim is made that the results obtained in this clinic are typical of what has been accomplished throughout New Jersey, for, obviously, opportunities and results have varied in each community.

Success in this specialized field does seem particularly dependent upon the personalities of the interviewers; some instinctively invite confidences, others repel them. The ability to meet patients on their own level and to give simple, rule-of-thumb instructions is an impor-

tant part of the case worker's equipment. These are characteristics which civil service examinations do not measure.

A CIVIL SERVICE TEST AND SPECIAL TRAINING FOR WORKERS

In choosing workers, the importance of training has been recognized. In New Jersey all appointments for venereal disease case work have been made from a list of nurses who have qualified through a civil service examination which was based upon training, experience, and knowledge of venereal disease control measures.

Each appointee has been given a three months' course in applied epidemiology at the Institute for the Control of Syphilis, University of Pennsylvania, of which John H. Stokes, M. D., is director. The course has been invaluable. It includes instruction in the nature, diagnosis, and treatment of the venereal diseases and the technic of interviewing. It is also coupled with supervised experience in obtaining epidemiologic information from the patients in the clinic and in following the problems of the infectious contact or delinquent patient into his home.

SCOPE OF STUDY

This paper deals with the experience in contact-tracing of one of the workers assigned by the New Jersey State Department of Health to the city of Camden during the period September 1, 1937, to April 30, 1938. Reports of the results of epidemiologic work in the literature of venereal disease control are few and limited in scope. They are confined almost exclusively to syphilis, and most of them have come from clinics operated in connection with teaching centers where, in general, higher standards of treatment are maintained than are found in the average public health clinic and where the patient is given more considerate handling than is ordinarily the case in clinics not sponsored and

supported by a teaching institution. This is the study of successful case-holding in syphilis and gonorrhea under the difficulties which will ordinarily be encountered in a public health clinic rather than a carefully controlled scientific study made under university auspices.

COMMUNITY CHARACTERISTICS

Camden is an industrial city which has had its full share of employment problems in the past few years. One-tenth of the total population of 119,000 are Negroes. There are two venereal disease clinics conveniently located in different sections of the city. One is at the West Jersey Homeopathic Hospital and the other at Cooper Hospital. Both of these are general hospitals supported by private funds and subsidized by the city or county but with no public funds ear-marked for venereal disease work. Both hospitals have conducted venereal disease clinics for many years, the larger being at Cooper Hospital where this effort in contact-tracing was made.

A study of Wassermann tests in the West Jersey Homeopathic Hospital made in 1934 indicates that there was not at that time an unusually high incidence of syphilis in Camden. In this hospital Wassermann tests on all hospital patients, private and ward, have been a routine practice since 1927. The case histories of the first 500 patients 16 years of age or over admitted to the hospital (exclusive of the out-patient department) and given a Wassermann test during the period 1927-34 were studied (6). This gave a total of 2,500 patients as a cross section of the adult hospital population over an eight-year period. About one-tenth of this group were Negroes, which is the same proportion that Negroes bear to whites in the general population. Six percent had Wassermann tests divided according to race as follows:

Color	Number treated	Percent positive
White.....	2, 227	3.9
Negro.....	203	29.0
Not stated.....	70	-----

Assuming that a higher rate would be expected for a hospital group than for well persons and allowing for the exclusion of children from the study, 6 percent positive results is not high. The State department of health has estimated from studies of certain groups made from time to time that syphilis afflicts 5 percent of the total population in New Jersey. Statistics recently compiled confirm this estimate (7).

There are no indications of an unusually high prevalence of syphilis in Camden or any reason to suspect an unusual incidence of gonorrhea.

METHODS AND CONDITIONS OF WORK

When, about the middle of August 1937, the worker first began her duties at Cooper Hospital clinic, 200 to 250 patients were being treated each week, although accurate reports of attendance are not available. The quarters were crowded, allowing no privacy for the patient. The physicians were not paid, and research work with its stimulus in improving the medical and social handling of the patients was out of the question under such circumstances. As in many clinics, treatment was inadequate according to the standard set up by the Cooperative Clinical Group and the United States Public Health Service,¹ and little or no effort was made to instruct the patient or to get his cooperation in tracing contacts. The local health department employed no venereal disease social worker.

Interviews with patients.—A room at the clinic where a fair degree of privacy is assured, was placed at the worker's

¹ The syphilis clinics of the University of Michigan, the University of Pennsylvania, Western Reserve University, the Johns Hopkins University, and the Mayo Clinic.

disposal for interviewing the patients during clinic hours. The worker tried not only to get from the patient being interviewed information about contacts but also to have the patient assume responsibility for arranging for the examination of the contacts reported by him, either by a private physician or by the clinic. The informant was also asked to help arrange to have the contacts call at the worker's office in the city health department at the city hall for an interview at some specified time. If the person named as a contact was to go to a private physician, the worker insisted upon having the name of this physician and checking with him to make sure that the person was in fact examined and that provisions for immediate treatment were made.

In cases where arrangements could not be made through the informant for the examination of the contacts, the worker sent a form letter on official department stationery directly to the alleged contact, summoning him to the office of the city health department at a specified time. About half of the examinations of contacts were arranged through the patients, most of these contacts being husbands, wives, or children. Almost half of the remainder came to the worker's office for an interview in response to a letter. The ready response to letters made it possible for the worker to interview a great many more persons than would have been possible by home visits to all. This was an important time-saver, as the worker was not familiar with the city and had to depend upon public transportation facilities in making home visits.

Interviews with contacts.—Contacts reported by patients were interviewed at the city health department located on the first floor of the city hall. The city hall is readily accessible to all sections of the city and the location and arrangement of the city health department are advantageous for interviewing. Along one side of the large reception room is a counter where the usual variety of licenses (marriage, restaurant, milk, ice,

and barber) and transcripts of birth and death certificates are issued. Due to the number of purposes to which this counter was put, there was no reason for embarrassment upon the part of the contact in coming to this office and asking at the counter for the worker by name, as instructed in the letter.

Methods of approach.—Tactful persuasion was relied upon in the interview with the patient and the contact. Every effort was made to have the patient understand the nature of his infection and the importance of treatment for himself and further protection of others and to secure his cooperation in finding other infected persons. The results reported in this paper were accomplished without police assistance, except in four or five instances in which the police cooperated promptly and efficiently in locating and bringing for examination persons who had evaded or defied the worker.

Selection of informants.—During the 8 months of the demonstration, the worker interviewed all new patients who came to the clinic and, as opportunity afforded, those patients who were already under treatment, choosing first the more recently infected and those most likely to spread infection. A total of 265 patients were interviewed. Except for an attempt to give priority to those most likely to transmit the infection, the group was composed of unselected clinic patients with active gonorrhea or with syphilis in various stages of the disease, latent cases being the most numerous.

EPIDEMIOLOGIC RESULTS

Of the 265 patients who were interviewed, 193 had syphilis and 72 had gonorrhea. Of these 265 patients, 237 (89 percent) named 410 contacts or about three contacts for each two productive interviews (table 1). The interviews with syphilitic patients were slightly more productive of epidemiologic results than were the interviews with gonorrheal patients. Of the 193 syphilitic patients

interviewed, 178 (92 percent) named 329 contacts or slightly less than two contacts per productive interview. Of the 72 gonorrheal patients, 59 (82 percent) named 81 contacts or slightly more than one and one-third contacts for each productive interview.

TABLE 1.—*Syphilis and gonorrhea patients classified by number and percentage who named contacts, and by number of contacts named per productive interview*

Disease	Number of patients interviewed	Patients who named contacts		Contacts named	
		Number	Percent	Number	Number per productive interview
Syphilis.....	193	178	92	329	1.85
Gonorrhea....	72	59	82	81	1.37
Total...	265	237	89	410	1.73

In the hope that the classification of common factors might contribute information of general interest and also be of assistance in directing the work of this particular investigator where it might be most effective, the syphilis and gonorrhea patients were grouped separately as to color, marital status, sex, and age. In addition, the contacts were classified according to the origin of the exposure as (1) the partners in illicit sex relations and (2) those exposed through association in the family including husbands, wives, brothers, and sisters. Success in finding and persuading each group to be examined and the results of the examination were also tabulated. The results of these analyses will be discussed briefly in the following paragraphs.

Syphilis—(a) *Patient interviews*.—More than two-thirds of the syphilitic patients were Negroes. They were somewhat less cooperative than the white patients. Of the Negroes, 91 percent were willing to give information and named an average of 1.8 contacts per productive interview. Of the white patients, 96 percent were found to be cooperative and named an average of two

contacts for each productive interview. Married persons and those separated or widowed were a better source of information than were single persons. Ninety-nine percent of the married persons and 97 percent of those widowed or separated named contacts, as compared with 83 percent of the single persons. The higher rate of productive interviews among the marital group may be partially accounted for by the fact that the marital partner or other members of the family of a syphilitic patient would be assumed by the case worker to be contacts whether or not they were actually named by the informant. This may account also for the slightly higher number of productive interviews reported by the married group (1.9:1), as compared with the single individuals (1.8:1), and also the fewer number of contacts (1.7:1) reported by the widowed and/or separated group.

Twice as many syphilitic women as men were interviewed. It was found that a significantly higher proportion of women gave information than did men, 98 percent of the women naming contacts as compared with 78 percent of the men. The number of contacts per productive interview was about the same for men and women.

When classified by age (ignoring the statistically insignificant age group under 10), it was found that the older persons cooperated more freely than did the younger groups. Of the age group 10 to 19, 88 percent named contacts, which increased to 95 percent in the ages 30 years and over. Those in the age group 30 to 39 gave the highest number of contacts (2.1:1), as compared with an average of 1.8:1.

When the patients were classified according to the stage of syphilis, it was found that information was secured from 96 percent of the latent patients interviewed, as compared with 74 percent of the primary and 79 percent of the secondary. The number of contacts per productive interview was practically the same in all three groups (1.8:1). These data are shown in detail in table 2.

TABLE 2.—*Syphilis patients interviewed classified by color, marital status, sex, age, and stage of disease; and by number and percentage who named contacts, and number of contacts named*

Classification of patients interviewed	Number of patients interviewed	Patients who named contacts		Contacts named	
		Number	Percent	Number	Number per productive interview
All.....	193	178	92	329	1.85
Color:					
White.....	54	52	96	103	1.98
Colored.....	139	126	91	226	1.79
Marital status:					
Single.....	81	68	82	124	1.82
Married.....	81	80	99	155	1.94
Widowed or separated.....	31	30	97	50	1.67
Sex:					
Male.....	66	53	78	97	1.83
Female.....	127	125	98	232	1.86
Age:					
Under 10 (congenital).....	2	2	100	7	3.5
10 to 19.....	49	43	88	74	1.72
20 to 29.....	79	73	92	132	1.79
30 to 39.....	38	36	95	76	2.11
40 to 49.....	20	19	95	35	1.84
50 and over.....	5	5	100	7	1.4
Stage of disease:					
Primary.....	23	17	74	31	1.82
Secondary.....	14	11	79	20	1.82
Latent.....	143	137	96	253	1.85
Congenital.....	13	13	100	25	1.92

In the small group of early cases (primary and secondary) the results approximate those reported in studies made at the University of Virginia and the University of Pennsylvania clinics. The primary and secondary cases give a combined total of 372 cases, 28 of whom gave information about 51 contacts, an average of 1.8:1 contacts per productive interview.

At the University of Virginia 119 syphilitic patients who were in the first year of infection, gave information about 196 contacts who had been exposed to infection, an average of 1.7 contacts per productive interview (8). In the study reported from the University of Pennsylvania clinic, 114 (56.7 percent) of 201 patients with early syphilis, gave information about 174 contacts, a rate of 1.5 contacts per productive interview (9).

Referring again to that part of table 2 which records productive interviews with 74 percent of the primary, 79 percent of the secondary, and 96 percent of the latent stage patients, it is interest-

ing to speculate as to the reasons for failure to secure information. Contact-tracing which originates with early cases offers the best opportunity to protect the public health, for the early cases were acquired recently from infectious persons of whom some may be assumed to be sexually promiscuous. Data about the 9 patients with early syphilis who would not, or could not, give information is listed in table 3 in order that the reader may draw his own conclusions as to the reasons for failure.

TABLE 3.—*Data about early syphilitics (primary and secondary stage) who were unwilling or unable to give information about contacts*

Patients	Age	Marital status	Sex	Color
1.....	24	Single.....	Male.....	Colored.
2.....	35	do.....	do.....	White.
3.....	19	do.....	do.....	Colored.
4.....	29	do.....	do.....	Do.
5.....	24	do.....	do.....	Do.
6.....	19	do.....	do.....	Do.
7.....	19	do.....	do.....	Do.
8.....	42	Widowed.....	do.....	Do.
9.....	16	Single.....	Female..	Do.

In recalling her unproductive interviews with these patients, the worker stated that she thought one or two might have given information with a little more time, that two had criminal records, and that two probably were not mentally capable of giving information. The significant differences between the cooperation of patients with early syphilis, as compared with those in the later stages of the disease, also suggest that the differences in cooperation noted

among these patients when classified by color, marital status, sex, and age, may be the result of the relative proportions of early syphilitics among them rather than the function of their sociobiologic characteristics. The number of cases in this study were too few to be statistically significant when these sociobiologic groups were broken down by stage and duration of infection. Consequently, this study can throw no further light on this premise.

TABLE 4.—Early and latent syphilis patients classified by epidemiologic results of interviews

Epidemiologic results	Origin of exposure	Early cases (primary and secondary)		Latent cases	
		Num-ber	Per-cent	Num-ber	Per-cent
Patients interviewed.....		37		143	
Patients who named contacts.....		28	76	137	96
Number of contacts named.....		51		253	
Number of contacts per productive interview.....		1.82		1.85	
Contacts in worker's territory.....	Sex.....	39			
	Family.....	8			
	Total.....	47		237	
Contacts examined.....	Sex.....	27			
	Family.....	8			
	Total.....	35		214	
Percent of total contacts in worker's territory.....			74		90
Contacts found infected.....	Sex.....	18			
	Family.....	0			
	Total.....	18		80	
Percent of those examined found infected.....			51		37
Positive cases per patient interview.....		0.49		0.56	

(b) Examination of contacts.—In table 4 are shown the number of contacts of both early and latent syphilis patients who were found and persuaded to be examined, together with the results of the examinations. Four of the 51 contacts of early syphilitic patients were referred to other health jurisdictions, leaving 47 in the worker's territory. Of these, 35 (74 percent) were examined and 18 (51 percent) were found positive. Of the 253 contacts of patients with latent syphilis, 16 resided in other health jurisdictions, leaving 237 to be traced by the worker. Of these, 214 (90 per-

cent) were found and examined, and 80 (37 percent) were diagnosed as syphilitic. Net results show an average of one infected person for each two of the 37 early cases interviewed, and a slightly higher rate for the 143 latent cases. No effort was made to check the results in the 20 contacts referred to other health jurisdictions for investigation. Adding the 25 contacts of the patients with congenital syphilis to the contacts of patients with early and latent syphilis, makes a total of 309 contacts of the

syphilitic patients in the clinic who were represented as living in the worker's territory. She found 281 (91 percent)

of these and persuaded them to be examined; of these 113 (40 percent) were found to have syphilis (table 5).

TABLE 5.—*Contacts reported by syphilis patients classified by origin of exposure, disposition, and results of follow-up and examination*

Origin of exposure	Number of contacts	Number referred to other health jurisdictions	Total number in worker's territory	Found and persuaded to be examined		Positive	
				Number	Percent	Number	Percent of those examined
Sex.....	134	16	118	103	87	50	49
Family.....	195	4	191	178	93	63	35
Total.....	329	20	309	281	90	113	40

Gonorrhea—(a) Patient interviews.—Seventy-two patients with active gonorrhea were interviewed (table 6). Of these, 59 (82 percent) named 81 contacts, an average of 1.4 per productive

interview. The gonorrhea patients were equally divided between the white and Negro races, there being no significant differences in the cooperation of one as compared with the other.

TABLE 6.—*Gonorrhea patients interviewed classified by color, marital status, sex, and age; and by number and percentage who named contacts and number of contacts named*

Classification of patients interviewed	Number of patients interviewed	Patients who named contacts		Contacts named	
		Number	Percent	Number	Number per productive interview
All.....	72	59	82	82	1.39
Color:					
White.....	36	29	81	36	1.24
Colored.....	36	30	83	46	1.53
Marital status:					
Single.....	47	36	77	49	1.36
Married.....	15	13	87	20	1.54
Widowed or separated.....	10	10	100	13	1.3
Sex:					
Male.....	55	42	76	57	1.36
Female.....	17	17	100	25	1.47
Age:					
10 to 19.....	21	18	86	28	1.5
20 to 29.....	45	37	82	50	1.35
30 to 39.....	5	3	60	3	1.0
40 to 49.....	1	1	100	1	1.0

As in syphilis, the married patients and those widowed or separated were a better source of information than were single persons. The married group named the most contacts with an average of 1.5 per productive interview.

Women comprised less than one-fourth the total number of gonorrhea patients interviewed but were 100 percent cooperative, naming an average of 1.5 contacts each. Of the men, on the other hand, only 76 percent were cooperative.

Among them, productive interviews yielded an average of 1.4 contacts.

All but six of the patients with gonorrhea were between the ages of 10 and

30. Slightly better results were obtained from the age group 10 to 19 than from the age group 20 to 29.

TABLE 7.—*Contacts reported by gonorrhea patients classified by origin of exposure, disposition, and results of follow-up and examination*

Origin of exposure	Number of contacts	Number referred to other health jurisdictions	Total number in worker's territory	Found and persuaded to be examined		Positive	
				Number	Percent	Number	Percent of those examined
Sex.....	69	9	60	53	88	32	60
Family.....	12	0	12	12	100	8	67
Total.....	81	9	72	65	90	40	62

(b) *Examination of contacts.*—The results of the follow-up and examination of gonorrhea contacts are shown in table 7. Nine of the 81 contacts named by patients infected with gonorrhea were in other health jurisdictions. Of the 72 in the worker's territory, 65 (90 percent) were located and persuaded to submit to examination. Forty of these (62 percent) were positive. It was found that gonorrhea patients named fewer contacts than did syphilitic patients. On the average, a little more than one new case

was found for each two of the 72 patients with gonorrhea. As in syphilis, the contacts of gonorrheal patients were classified according to the origin of the exposure. The number of sex contacts was five times the number of family contacts. All of the 12 family contacts were examined and 8 (67 percent) were found to be infected. Of the 60 sex contacts in the worker's territory, 53 (88 percent) were examined and 32 (60 percent) were found to be infected.

TABLE 8.—*Contacts reported by syphilis and gonorrhea patients classified by disposition and results of follow-up and examination*

Disease contacted	Number of contacts	Number referred to other health jurisdictions	Total number in worker's territory	Found and persuaded to be examined		Positive	
				Number	Percent	Number	Percent of those examined
Syphilis.....	329	20	309	281	90	113	40
Gonorrhea.....	81	9	72	65	90	40	62
Total.....	410	29	381	346	90	153	44

SUMMARY

The epidemiologic program for the control of syphilis and gonorrhea first undertaken in New Jersey in 1922, has been extended with the aid of Federal funds under Title VI of the Social Security

Act. This is a report of a recent demonstration of contact-tracing in Camden.

In the course of 8 months' work in a public health clinic 265 patients with either active gonorrhea or syphilis in its various stages were interviewed. Of these patients, 89 percent gave informa-

tion about contacts, an average of 1.7 contacts per successful interview. The patients who were interviewed were classified by age, sex, color, marital status (in cases of syphilis the stage of the disease was also given) to determine whether or not markedly better cooperation might be expected from any group. Contacts were classified according to the origin of the exposure as (1) illicit sex, or (2) family. The variation in cooperation and the epidemiologic results among these groups is not great enough to warrant the singling out of any one for special effort. It is interesting to note that the number of positive cases found per patient-interview was a little greater among the group with latent syphilis than among those in the early stages of the disease.

A higher percentage of all those with syphilis gave information than did patients with gonorrhea, but success in finding and persuading contacts to be examined as a result of this information was proportionately the same in both diseases; 90 percent of the contacts named by both groups were found and examined. A higher percentage of infections was found among the contacts of gonorrheal patients than among the contacts of syphilitic patients. In the former instance, 62 percent were infected, as compared with 40 percent in the latter.

Net results as interpreted from the number of infected persons found by interviewing unselected patients in this public health clinic and following up information secured from them was about the same among the patients with syphilis as among those with gonorrhea. One hundred ninety-three patients who had syphilis were interviewed and 113 positive cases found, more than one case for every two patients interviewed; 72 patients who had gonorrhea were interviewed and 40 infected persons found. In addition, 29 contacts reported by these patients were referred to other health officers for investigation.

This experience in Camden is another indication that the epidemiologic program as carried out in some communities in New Jersey is a practical method of finding persons infected with syphilis and gonorrhea.

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Acknowledgment. Credit for the success of this demonstration of contact-tracing should go chiefly to Mrs. Sylvia R. Rosen, R. N., the "worker" of the Division of Venereal Disease Control, New Jersey State Department of Health, who carried on energetically and with intelligence and enthusiasm to make these accomplishments possible.

A Note on the Influence of Open or Closed Water Bath Incubation in the Sensitivity of the Hinton Test in the Serodiagnosis of Syphilis

RUTH M. MYERS, M. S., Baltimore, Md.

BECAUSE the Hinton test in our laboratory had yielded only 73.2 percent sensitivity in comparison with Hinton's 83.9 percent in the evaluation studies conducted by the U. S. Public Health Service in 1938, Dr. Hinton was asked to send us a series of negative and very weakly reacting specimens for check purposes. Accordingly, serums were sent in groups of 10 to 15, twice a week for a period of about 5 weeks. At the start it was very evident that our results were considerably less sensitive than those of Dr. Hinton's laboratory. By centrifuging every test we found that we could more closely approximate Hinton's sensitivity, but his procedure designates centrifugalization only for those tests giving questionable reactions on first inspection. Thinking that our indicator might be somewhat undersensitive, we tested several series of specimens in duplicate with two indicators one of which had been approved by Hinton. Less sensitive results were obtained consistently with both indicators. During discussion of the problem, a question was raised as to what difference there might be between incubation of the tests in an open bath, as used in Hinton's laboratory, and incubation in a closed bath as used in our laboratory. Duplicate tests were continued on all specimens and one set was incubated in an open bath, the other in a closed bath. The reactions of tests incubated in the open bath were definitely easier to read than those in the closed bath. In many instances tests incubated in the open bath gave definite positive reactions whereas parallel tests incubated in the closed bath gave negative reactions. Some open bath positive

tests occurred on specimens which gave closed bath doubtful results. Also, open bath tests were doubtful on a number of specimens in which closed bath results were negative. It was found that the results obtained by open bath incubation agreed closely with Dr. Hinton's. A more compact floc seemed to form giving more clear-cut results, and centrifugalization had to be resorted to rarely in making the routine readings. Specificity was not decreased by this increase in sensitivity.

This study, conducted on a series of specimens tested both at the Boston Dispensary and the Maryland State Department of Health, seems to us to indicate the importance of technical details and the necessity for precise stipulation of and observance of technical details in the performance of serologic tests for syphilis.

From the Bureau of Bacteriology, Maryland State Department of Health, Baltimore.

PUBLIC HEALTH ADMINISTRATION

Educational and training qualifications for venereal disease control officers.
Adopted by the Conference of State and Territorial Health Officers at Washington, D. C., April 25, 1939.

Basic educational requirements and special qualifications shall be:

1. The earned degree of Doctor of Medicine from a reputable medical school and eligibility to examination for medical

licensure in the State where service is to be rendered.

2. Not less than one year of general clinical experience gained preferably in a hospital of acceptable standards.

3. The satisfactory completion of not less than one academic year of work in a recognized postgraduate school of public health, or, in lieu of this special training, two years of full-time public health work.

4. A period of at least six months intensive training in the clinical management of the venereal diseases in a well-organized postgraduate course, or its equivalent¹ if instruction in the clinical management of the venereal diseases constitutes a stipulated part of the course of training in the school of public health.

Gonorrhea in the Male and Female. P. S. Pelouze, M. D., Assistant Professor of Urology, University of Pennsylvania; Consulting Urologist to Delaware County Hospital; Special Consultant to U. S. Public Health Service. Philadelphia, W. B. Saunders Co., 1939. Third edition, revised.

This book "Gonorrhea in the Male and Female" is too well known to require an introduction to the medical profession. In this third edition the author has again placed in the hands of the profession the most modern views on the diagnosis, treatment, and public health aspects of gonococcus infections. He has presented a comparison of various points of view and expresses a warning note not to adopt procedures and methods of treatment without adequate proof from reliable studies.

The third section of the book "The Medical Profession and Gonorrhea Control" is entirely new. The author discusses the epidemiology of gonorrhea and the extent of the gonorrhea problem in the United States as compared with other diseases. He points out "the sins of omission and commission" of the med-

ical profession and suggests methods for their correction.

In discussing the gonorrhea dispensary the author points out the abuses encountered on the part of the patient who seeks free treatment when he can afford to pay, and the physician who fails to direct patients who cannot afford to pay for treatment to the dispensary. He also points out the urgent need for well conducted dispensaries for the treatment of gonorrhea but states that definite improvement in many of them has been made during the past decade.

In the last few chapters he offers suggestions for the solution of many problems and discusses the relationship of the druggist, the prostitute, and the public to the control of gonorrhea.

You Can End this Sorrow—Folder No. 3—has recently been issued by the United States Public Health Service. It deals with the problem of the prevention of congenital syphilis. Copies can be obtained from the Superintendent of Documents, Washington, D. C. at the price of \$1 per 100 copies.

Antenuptial blood tests in Wisconsin. W. F. Lorenz. Wisconsin M. J., Madison. Apr. 1939, 38: 318.

The Wisconsin statute which requires every applicant for a marriage license to show a negative "Wassermann test" of the blood became effective on July 1, 1937. This test must be made within 15 days prior to the time of application.

Some difficulty was experienced because the laboratory was required to certify as to the "person" whose blood had been sent in for examination, but this was obviated by the physician certifying as to the person and the laboratory as to whether the specimen received was positive or negative. This procedure may have to be legalized. The Attorney General has ruled that the term "Wassermann test" is used in a generic sense.

From July 1, 1937 to December 30, 1938, the laboratory has received 46,431

¹ Not less than one year of work in a recognized school of public health.

blood specimens marked "for marriage license" from 45,992 individuals. Since during this same period 66,408 persons were married in Wisconsin it may be assumed that approximately 70 percent of the tests of those who married were made at the State laboratory. The laboratory reported 295 persons as having a distinctly positive reaction for syphilis, or about 0.6 percent of the marriage applicants. Adding 120 cases, an estimate for the approximately 20,000 persons not examined through the State laboratory, would give a total of 415 cases of syphilitic infection found in the State by the antenuptial examination in 18 months. The 295 cases were divided equally between men and women which is contrary to the general finding.

These cases of syphilitic infection which are discovered at the antenuptial examination very evidently, Lorenz believes, represent persons who were unaware of their infection and who, therefore, have been and would be untreated. There would be many cases of congenital syphilis, many of extragenital chancre, and very likely many without primary lesion. From a medical standpoint such cases are especially serious; they are more vulnerable to the later serious forms of syphilis. It must be conceded, therefore, that this law has accomplished much good even though it has been a shocking experience for some unfortunate individuals.

All blood specimens that react to any degree in the first sensitive flocculation test are retested with a complement fixation method. Unless definitely instructed to do so by the attending physician the results of the test are reported only to the physician. Because a positive blood test for syphilis does not always mean an active syphilitic infection, Lorenz suggests a possible amendment to the present law whereby there may be an appeal from the mere laboratory test by a presentation of the facts to some sort of a medical commission.

The problem of the venereal diseases.

Editorial. M. J. Australia, Sydney. Apr. 8, 1939, 1:551.

Legislation directed toward the control of venereal diseases has been enacted in every State of Australia except South Australia during the past 20 years, and the writer feels that it is time to inquire as to whether the expected results have been obtained. Available evidence suggests that there has been a decline in the incidence of syphilis, though apparently this has been due to the modern methods of treatment; the sources of the disease cannot be regarded as being under control since recrudescences of acute infection occur from time to time. Gonorrheal infections give every indication of a tendency to increase. Whether there will be beneficial results from the treatment with the sulfonamide group of compounds can be determined only by further experience.

The Scandinavian countries were the first to organize a comprehensive program, including legal compulsion, for the control of syphilis. However, experience and investigation of other countries now suggest that compulsory treatment is not the major factor in influencing results. Success depends upon the close coordination of a number of factors, the most important being the provision of adequate facilities for efficient diagnosis and for early treatment which must be available free of charge to all sufferers. The Scandinavian arrangements work with smoothness—the people have a highly developed and practically universal respect for law and great respect for the medical profession. In the United States there is no restriction of the liberty of the subject, no great facilities for treatment, and a high incidence of venereal disease. Between the two extremes there are other countries, including Australia, with incomplete organization and with results which fall short of what is possible.

Within limits public health can be purchased, but methods must be found to

overcome public apathy and indifference and to secure the full cooperation of all concerned including teamwork among the members of the medical profession.

Contact investigation and the early recognition of syphilis. E. Gurney Clark and Rudolph H. Kampmeier. *Urol. & Cutan. Rev.*, St. Louis. Mar. 1939, 43: 169.

In the Vanderbilt Hospital Clinic one of the authors has devoted his entire time to the epidemiologic aspects of syphilis and has been aided by trained social workers. These conditions cannot be regularly duplicated by the private practitioner, but the results of this experience indicate what can be done by epidemiologic investigation. Success or failure is determined by the extent to which full cooperation of the patient is obtained, and the private practitioner is in a particularly favorable position to obtain this cooperation. The proper presentation of the problem often results in the patient's bringing in contacts for examination. Even though the effort in many cases is futile the practitioner is otherwise repaid for his time by having for treatment a more understanding, loyal patient.

A study of the results obtained during the first 6 months of the special contact investigation at the clinic is interesting. During this period 122 patients with acute or early latent syphilis came to the clinic. From these patients the names of 368 family and sexual contacts were obtained. Epidemiologic efforts resulted in the discovery of 100 infectious or potentially infectious cases among these contacts. This number represents the proportion of 4 early cases of syphilis among the contacts to every 5 initial cases. Of the 100 contact cases, 37 were family contacts and 63 extra-familial.

An appeal to the women of America to help stamp out congenital syphilis.

D. W. Byrd and E. D. Burke. *J. Nat. M. A.*, New York. May 1939, 31: 127.

In seeking the help of all the people in wiping out the scourge of syphilis

from American homes and life, there must be full knowledge of the necessity of continued treatment and observation by persons qualified for this work, not by quacks and drug clerks. Home and school must explain and teach sex life. Recently while visiting the office of a doctor who for 16 years had routinely taken blood tests of each patient, the authors found a record of 10,455 tests with 2,708 positive for syphilis. This doctor had given himself a fine opportunity for helping his fellow man.

Congenital syphilis is a pressing problem. With 15 percent of the American Negro youth with inherited syphilis and 18 percent of the colored women of child-bearing age infected, the problem is for all races and classes. The surest and best way to find syphilis in a pregnant woman is by repeated blood testing. Pregnancy destroys for the most part the external manifestations in syphilis, but adequate treatment early in pregnancy assures a normal child in more than 10 cases out of 11. Every woman is advised to consult a physician in the early stages of pregnancy so that she may be sure of giving her unborn child his rightful heritage of health.

History of previous pregnancies. W. Z. Bradford. *South. Med. & Surg.*, Charlotte. Apr. 1939, 101: 178.

The obstetric history is a much neglected but a valuable method of recognition and prevention of obstetric pathology. This information can be obtained by every physician who will take time to ask questions and listen. The history of the birth of a macerated fetus always demands thorough investigation for the possible presence of syphilis.

Social service at the venereal disease treatment centers. Editorial. *Health & Empire*, London. Mar. 1939, 14: 1.

If the free treatment centers are to achieve full success it is essential that every effort be made to induce patients to continue treatment until pronounced fit for discharge and to obtain the attendance at the clinics (or elsewhere) of the contacts whether or not such con-

tact is the source or the victim of infection. Out of 367 recent infections with gonorrhea the untraced contacts were 242, and only 125 contacts were brought under medical care. There were 75 men and 35 women who discontinued treatment. Neither health center concerned had a trained almoner or social service worker.

Granted that the number of infected contacts does not necessarily equal the number of patients attending clinics and that some of the contacts may be receiving treatment privately or at other clinics, the figures show that the number of contacts under treatment is far too small and the proportion not completing treatment far too high. The remedy lies in the appointment of special almoners able to induce recalcitrant patients to return for further treatment and to trace contacts and persuade them to seek diagnosis. Personal education and persuasion is needed in these cases. The problem is not insoluble in that where social service is available and the personal methods of education and persuasion can be utilized it has proved possible to secure the voluntary attendance at the treatment centers of the majority of partners for examination and, if necessary, for treatment.

Social hygiene and rearmament. Brit. M. J., London. April 22, 1939, 1: 834.

The British Social Hygiene Council, which has recently published its 23d annual report, was formed as the National Council for Combating Venereal Diseases. Sir Walter Langdon-Brown says in a foreword to this report that venereal disease is only a special instance of the evils resulting from a failure on the part of individuals to discover their role as members of society. The remedy is education of a positive and not merely a preventive kind. The outstanding needs in relation to the scheme of treatment under local authorities are (1) more continuous educational enlightenment particularly among women; (2) an almoner service at every treatment center to follow up contacts and cases discon-

tinuing treatment, and a recognition that this service is as essential for male patients as for female patients; (3) positive health teaching and sex guidance for adolescents and young adults of both sexes.

The total number of gonorrhea cases under treatment has increased slightly in England and Wales and decreased in Scotland. For the first time in many years the number of attendances at treatment centers has decreased.

Rearmament may have an important bearing on certain aspects of social hygiene. The British Air Force has expanded greatly, and new training centers and aerodromes have been established in what were predominantly rural areas. Many new munitions factories have been established, also. This redistribution of the population may lead to an increase of sexual promiscuity and of venereal infection. Treatment centers are few and far between in the country districts where camps and factories have been set up, and facilities for guidance in sex behavior are likely also to be lacking. It is considered that where, owing to these conditions, an increase in social hygiene education and social service is needed, or new civil treatment centers are necessary as a result of the establishment of service camps, their cost should be met by a grant from national funds rather than from local rates.

Syphilis and marriage. Andrew B. Jones. J. Missouri M. A., St. Louis. May 1939, 36: 196.

Some of the problems to be considered in deciding the question of marriage of a person who has or has had syphilis are (1) the duration of the infection, (2) the course of the individual infection—relapse, neurosyphilis, etc., (3) type and amount of treatment, (4) the lack of any criteria by which one may pronounce the patient completely cured, (5) the willingness of the patient to return for examination and treatment, (6) the necessity of the partner knowing about the previous infection in the mate, and (7) treatment of the wife at the

time of pregnancy regardless of serologic or other evidence of infection.

Keyes states that 8 out of 10 persons with syphilis cease to be infectious after 3 years even though they do not receive treatment; 99 out of 100 cease to be infectious after 4 years, and the proportion of infections from persons with syphilis of more than 5 years standing is infinitesimal. He also states that the chances for marital infection are 12 to 1 during the first year of the disease, 5 to 2 in the second year, 1 to 4 in the third year, and very slight after the fourth year whether or not the patient has been well treated. He believes that marriage of a person with syphilis is permissible after 5 years if during the last 2 years the patient has had no symptoms.

The presence or absence of syphilis is not proved by a serologic test. A negative blood reaction does not mean that the patient cannot transmit the disease. No patient should be permitted to marry without an examination of the cerebrospinal fluid. It is imperative that both patient and spouse should be examined for syphilis at regular intervals as long as they live. In spite of the outward appearance of good health, the infected partner should be given a course of treatment at intervals throughout life.

The wife of a husband with syphilis should be given active antisyphilitic treatment during the entire course of her pregnancy whether or not she shows any evidence of infection. The children of these persons should be examined carefully. About 50 percent of children with congenital syphilis do not show physical signs of the disease until about the time of puberty or adolescence.

To be of value an examination must include careful history of the course of an illness; amount, kind and length of treatment; habits of the patient; serologic tests of the blood; careful examination of the cerebrospinal fluid; and complete physical and neurologic examinations. In some cases an additional period of observation is desirable.

High proportion of mothers tested for syphilis during pregnancy. Health News, Albany. Apr. 24, 1939, 16: 65.

The law requiring a blood test for syphilis in every case of pregnancy took effect in New York State in March 1938, but only since January 1, 1939, has a statement as to whether or not such a test was made been required on the birth certificate. During January the test was reported as having been made on 93.5 percent of the births in the entire State outside of New York City; in 68.4 percent of the cases the test was made prior to delivery and in 25.1 percent at the time of delivery.

There were 6,837 births in upstate New York during January, and of these 5,003 were in hospitals. The birth certificates show that in only 1.9 percent of the births in hospitals no test for syphilis was made, while for those in private dwellings the percentage was 13.9. The proportion of mothers who were tested for syphilis during pregnancy was greater in the urban than in the rural area, the percentages being 71.5 and 65.2 respectively. The percentage of tests made during delivery was greater in the rural area, 26.6 as compared with 23.7, while the percentage of cases in which no test was made or no information regarding the test was given was 8.2 in the rural, almost double the corresponding figure (4.8) for the urban area.

Syphilis control, the medical problem.

F. W. Caudill. Kentucky M. J., Bowling Green, Apr. 1939, 37: 138.

The author discusses the incidence, control, treatment, diagnosis, and cost of syphilis with special emphasis on the occurrence of the disease in Kentucky.

He estimates that in Kentucky there are 132,000 persons who now have, have had, or will have syphilis, and 11,000 new cases are being recognized annually in the State. Most of the new cases are contracted by persons between the ages of 20 and 30 years. The life of each of these infected persons is shortened an average of 5 years. About 20,000 po-

tential mothers in Kentucky now have or have had syphilis. Probably 2,700 of the 30,032 deaths in Kentucky in 1937 were due, directly or indirectly, to the disease. Syphilis affects the health and wellbeing of more citizens in Kentucky than any other single communicable disease.

From 60 to 65 percent of currently treated cases of syphilis are in the care of the private medical practitioners of the State, and a large portion of the remaining cases are being treated in clinics in charge of physicians who either volunteer their services or occupy official public health positions.

Of the 56,000 births in Kentucky in 1936, 2,000 were stillbirths. Of these stillbirths, about 500 (25 percent) were due to syphilis. If the presence of syphilis in the mothers who gave birth to these 500 dead babies had been detected before the fifth month of pregnancy and the mothers had been given adequate treatment from time of detection to delivery, 10 out of each 11, or 450, of these babies would have been saved.

At current prices, it is estimated that the cost of treating properly an early case of syphilis is between \$250 and \$300. Few patients can afford to pay for adequate treatment. The average physician cannot afford to pay for drugs, equipment, and office overhead and then treat cases of syphilis for nothing. Many physicians feel that a case of syphilis can be treated at a moderate price. More patients can afford the lower cost and the patients, treated at prices which they can afford to pay, are able to take more treatments. Thus, it is reasonable to assume that a moderate price for treatment will actually work financial gain to the physician.

Both the private practitioner and the health officer have a profound responsibility in educating the people concerning syphilis. Close cooperation between the two is very important.

Bradley, in discussing this paper, stated that in the early days of salvarsan

and neosalvarsan therapy, patients were charged huge prices for treatment. Physicians considered it unusual to give the intravenous injections and charged accordingly. The result was that patients would get 2 or 3 injections of salvarsan or neosalvarsan at \$10 to \$25 an injection, and then they could no longer afford to continue treatment.

Free venereal service given 52,040 monthly. California second to Massachusetts in providing treatment. San Francisco News. Mar. 7, 1939. Reprinted in California and West. Med., San Francisco. Apr. 1939, 50:307.

Medically indigent patients were given an average of 52,040 treatments for venereal diseases each month during 1938 in California clinics and State institutions as part of the venereal disease control program of the State department of public health. This placed California second among all the States in providing treatment for venereal disease patients who are unable to pay the cost of medical care. Massachusetts was listed as first by the United States Public Health Service in the number of clinic treatments, with a monthly average of 79,170 while New York ranked third with 51,746.

In Los Angeles, 245,935 treatments for these diseases were given in public clinics in 1938; in San Francisco the number was 125,124.

The State director of public health of California, estimated that, in addition to the 624,450 treatments given during 1938 in the clinics of California, private physicians gave patients 1,580,000 treatments for syphilis and gonorrhea.

The California State Department of Public Health distributes free antisyphilitic drugs to private physicians for the treatment of patients who are able to pay only part of the cost and for those who do not live near clinics.

LABORATORY RESEARCH

Study of the etiology of lymphogranuloma inguinale. Passage of the virus into the brains of mice experimentally infected through the eye. Gian. Battista Cottini. *Riforma med.*, Roma. Dec. 24, 1938, 54: 1957.

In previous work the author showed that lymphogranuloma virus inoculated into the brain could be demonstrated later in the eyes and internal organs of rabbits. In this article he studies the route followed by the virus when injected into the cornea. A first series of studies on 10 mice was completely negative. After an incubation period of about 10 hours the animals all showed a local inflammatory reaction which in some cases grew much worse from secondary infection and in others healed, but blindness resulted in a maximum time of 8 days. No general symptoms developed, and there were no positive results in smears from the brains of these animals.

In 10 other animals the virus was introduced directly into the anterior chamber of the eye. All the animals reacted within 24 hours. Five died within 2 days and a sixth after 3 days without any special symptoms. Smears of their brains and inoculations into other animals were negative. Of the remaining 4, 2 died after 15 days with no special symptoms and negative laboratory and biologic results. But the other 2, after 8 days, showed slight paresis of the hind legs and died within 24 hours. Autopsies were done immediately and their brains examined in smears and by means of inoculation into other animals.

Both these methods of examination were positive. A few very characteristic granules were found in smears stained with Victoria Blue R and Giemsa stains. The animals into which the virus was

inoculated died after a week, and the virus was found in smears of their brains.

The characteristics shown by the passage of the virus were very much like those found previously in herpes virus. But in contrast with the herpes cases there were very few positive reactions in the brain in comparison with the constancy and intensity of the corneal reactions which would indicate that the virus is epitheliotropic rather than neurotropic. The author believes that the virus, like that of herpes, follows the lymphatic tracts which accompany the nerves in its passage from the periphery to the brain. The virus seems to find a good medium for development in the brain centers. In this, too, there is a marked resemblance to herpetic virus.

The effects of molecular oxygen and sulfhydryl compounds on the antispirochetal action of arsenic, bismuth, and mercury compounds in vitro. Harry Eagle. (*Proc. Am. Soc. Pharmacol. and Exper. Therap.* April 26-29, 1939). *J. Pharmacol. & Exper. Therap.*, Baltimore. May 1939, 66: 10.

The antispirochetal action in vitro of arsenoxide (m-amino-p-hydroxyphenyl-arsenoxide) and bismuth compounds was unaffected by the removal of molecular oxygen and is probably due to these compounds as such. In marked contrast, neoarsphenamine, which is highly spirocheticidal when dissolved aerobically, was negligibly so when dissolved and tested under nitrogen in the absence of oxygen. Its relatively marked antispirochetal action when tested aerobically (25 to 60 times that observed under nitrogen) is apparently due to its oxidation by molecular oxygen to other directly spirocheticidal compounds. This oxidation did not require the presence of tissue derivatives and proceeded so rapidly that solutions became actively spirocheticidal within 3 to 5 minutes.

Commercial arsphenamine and silver arsphenamine were intermediate between arsenoxide and neoarsphenamine, in that although two-thirds to seven-eighths of

their antispirochetal activity in vitro was due to oxidation products, there was a small but significant residual activity in the absence of oxygen. In the case of arsphenamine, a large part of this residual activity was accounted for by arsenoxide or arsenoxide-like substances present as an impurity.

Sulfhydryl compounds (cysteine, glutathione, and thioglycolic acid) added in sufficient excess to arsphenamine, arsenoxide, bismuth, or mercury compounds, almost completely abolished their antispirochetal action in vitro. The large excess which was necessary to cause complete inactivation of the arsenicals suggests that the addition compound may be readily hydrolyzed. Thiamin chloride and methionine, which contain a —S— rather than a —SH group, had no inhibitory effect.

These findings are of interest in relation to the thesis that the antispirochetal action of arsenic, bismuth, and mercury compounds may depend on their common affinity for sulfhydryl groups in *Treponema pallidum*.

Experimental study of the injuries to the blood caused by arsenobenzols. M. Lancellotti. Policlinico (sez. med.), Roma. Nov. 1, 1938, 45:573.

The author studied the blood changes in the same groups of animals in which Montanaro studied the lesions of the blood-forming organs—15 rabbits and 30 guinea pigs. Large doses, even up to sublethal ones, were given at intervals of 5 days and up to a maximum of 10 injections.

After a slight inconstant increase in the number of red cells probably due to reaction on the part of the bone marrow there was a characteristic decrease which was not very serious and which was succeeded in a few days by increased production of red cells with the appearance in the blood of immature cells, anisocytosis and poikilocytosis, basophil granulations, polychromatophilia, etc. The decrease in hemoglobin resulting from the decreased number of red cells was more than compensated for by the

appearance of macrocytes and spherocytes containing so much hemoglobin that the color index was increased. As the increase in the proportion of hemoglobin was greater the smaller the number of erythrocytes this was evidently a defense reaction.

Among the white cells there was an absolute and relative decrease in neutrophil granulocytes and an increase in the relative and sometimes the absolute number of mononuclears and lymphocytes. The values found experimentally coincided very closely with those in two clinical cases recently presented before the medico-surgical society of Modena.

As all the blood lesions were moderate and transitory the author believes that the few cases of agranulocytosis seen clinically in proportion to the very large number of cases treated with arsenic must be due to individual predisposition rather than to a constant injurious action of the arsenobenzols.

The spirocheticidal action in vitro and mouse toxicity of a series of monosubstituted phenylarsenoxides. George O. Doak and Harry Eagle. (Proc. Am. Soc. Pharmacol. and Exper. Therap. Apr. 26-29, 1939). J. Pharmacol. & Exper. Therap., Baltimore. May 1939, 66:9.

A series of 19 compounds was prepared consisting of phenylarsenoxide and its OH, CH₃, NH₂, COOH, Cl, and NO₂ derivatives. The o-, m-, and p- compounds were prepared in each instance. The m-OH, m-NH₂, o-Cl, and m-Cl derivatives have apparently not been previously described. With the exception of the three COOH compounds, the position of the substituent group had relatively little effect on either spirocheticidal activity or toxicity. However, the several types of compounds varied greatly in both respects. Thus, the antispirochetal action of the CH₃ compounds as determined in vitro with a suspension of *Treponema pallidum* was slightly higher than that of the parent phenylarsenoxide; that of the OH, Cl, and NH₂ compounds was approximately 65 to 100 percent that of

phenylarsenoxide; the o-COOH, m-COOH, and p-COOH derivatives were 25, 15, and 5 percent as active respectively; while the o-NO₂, m-NO₂, and p-NO₂ derivatives were practically inert. The toxicity of these compounds on intraperitoneal injection into white mice was also determined. In general, the mouse toxicity paralleled antispirechetal activity.

The antispirechetal activity seems to be determined primarily by the arsenoxide group, and the substituent group evidently serves only to modify that activity, usually in an inhibitory sense. Experiments on the therapeutic activity and toxicity of these compounds in syphilitic rabbits are now in progress.

Sulfanilamide cyanosis in chickens, pigeons and mice, and its treatment with methylene blue. Arthur P. Richardson. (Proc. Am. Soc. Pharmacol. & Exper. Therap. Apr. 26-29, 1939). J. Pharmacol. & Exper. Therap., Baltimore. May 1939, 66: 29.

Chickens and pigeons given orally 0.5 to 2.0 gm. sulfanilamide per kilogram daily, and mice fed a diet containing 1 or 2 percent sulfanilamide (1.4 to 2.3 gm. per kilogram) became cyanotic in 3 to 6 days. Drawn blood was dark after aeration. The percentage of non-oxygen-carrying pigment as determined by the difference between blood iron and oxygen capacity increased from a control level of 0 to 4.0 percent of total pigment before administration of sulfanilamide to 10.0 to 44.0 percent afterwards. Spectroscopically all bloods showed an absorption band at 630 μ which disappeared on the addition of sodium cyanide or sodium hydrosulfite. The addition of methemoglobin to normal blood in concentration of 10.0 to 35.0 percent resulted in cyanotic blood which matched in color that obtained in experimental animals, indicating that in these species the cyanosis can be explained by formation of methemoglobin. Because of the high blood level of sulfanilamide in these experiments, the results presented do not contradict those obtained by Marshall and Walzl and by

Chesley who reported only traces of methemoglobin in cyanotic patients except when the blood concentration was high.

Cyanosis established in chickens persists for at least a week after discontinuing the drug. However, injection of methylene blue (5 to 10 mg. per kg. intravenously) decreases the nonoxygen-carrying pigment about 50 percent for 8 to 24 hours in most birds. Methylene blue is also effective in vitro in converting methemoglobin to oxyhemoglobin, but only in the presence of plasma, indicating the necessity for some intermediate substance for this action.

Experimental study of lesions of the blood-forming organs caused by arsenobenzol. E. Montanaro. Policlinico (sez. med.), Roma. Nov. 1, 1938, 45: 553.

The author studied the effect of arsenobenzol on the blood-forming organs and the blood in rabbits and guinea pigs. He discusses the effects on the organs, illustrating them with microphotographs.

One group of 6 rabbits were given subtoxic doses of 0.10 gm. arsenobenzol per kilogram of weight into the marginal vein of the ear at intervals of 5 days. Blood examinations were made before the injections and 1, 2, 3, 4, and 5 injections given to the different animals. They were then killed and the organs examined histologically in order to determine the very beginnings of changes. The second group of 8 rabbits were given 10 intravenous injections each of 0.10 gm. per kilogram of weight, the blood being examined before treatment and complete histologic examination made after they were killed. Two of the animals died, one of shock after the first injection and one of hemorrhage after the second. The others lived till the end of the treatments without any serious signs.

A group of 30 guinea pigs were given sublethal doses of 0.10 gm. arsenobenzol subcutaneously which were later reduced to 0.05 and then 0.025 gm. The doses were given at intervals of 5 days.

Eleven of the animals died after the first or second injection, and 9 died later during the injections. The other 10 were killed in pairs after each injection beyond the fifth.

The findings were about the same in the organs of the first and second groups and of the surviving animals of the third group. The organs, particularly the liver, kidneys, and suprarenal glands showed degeneration changes with cloudy swelling and sometimes necrosis. In a second phase there is habituation to the drug and then a phase of repair similar but not equal in degree to a true cirrhosis.

The changes in the blood-forming organs followed those in the above-mentioned more sensitive organs. In the bone marrow the blood-forming function showed reactive and compensatory hyperfunction. There was marked hemolysis in the spleen followed by the appearance in the blood of young nucleated red cells. There was a moderate lymphoid reaction. The production of granulocytes was moderately and temporarily reduced but not abolished. The production of basophils and eosinophils was stimulated and the production of platelets only slightly changed. These changes bring about a plastic hypochromic secondary anemia due to increased hemolysis and a granulocytopenia due chiefly to temporary hypofunction of the bone marrow. This hypogranulocytosis is not, the author thinks, a step toward granulocytosis for in his case there was no true agranulocytosis but a restoration to normal after a period of adjustment.

The sensitiveness of the organs to the drug varied greatly in different individuals.

Attempts to infect rabbits, rats, and mice with gonococci. W. Schäfer and E. Walther. *Ztschr. f. Hyg.*, Berlin. Mar. 18, 1939, 121: 517.

The authors attempted to produce infection with gonococci in rats and rabbits by first decreasing their resistance by various methods. They found that

gonococci injected intraperitoneally into rats could be demonstrated for a longer period of time if these rats had been previously X-rayed. They believe that this occurs as a result of the decrease in the number of leukocytes which follows the application of the X-ray. Gonococci which had gone through several animal passages did not produce typical gonorrheal ophthalmia of the rabbit eye. Sensitization with bile, gonococcus toxin, injury of the eye with X-rays and alpine light also did not produce this result. Rabbit antigonococcus serum which contained agglutinating antibodies failed to protect mice against the intoxication with lethal amounts of gonococci. Sulfanilamide, disseptal C, and uliron also failed to protect mice in this way even when they had been previously immunized with rabbit immune serum or by immunization with sublethal amounts of gonococci. Mice which had received preliminary treatment with certain phenyl sulfoxides (especially 4 nitro-4-amidodiphenylsulfoxide and 4 nitro-4-acetylaminodiphenylsulfoxide) had 15 to 30 percent less gonococcus intoxications than the control animals. Further study is required to determine whether the intraperitoneal injection of large, lethal doses of gonococci in mice and rats constitutes a suitable method for testing chemical substances for their effectiveness in gonorrheal therapy.

PATHOLOGY

Early acute arsenical erythemas. A study of eleven cases of the "erythema of the ninth day" of Milian. Orlando Cañizares and Evan W. Thomas. *Arch. Dermat. & Syph.*, Chicago. May 1939, 39: 867.

The exact nature of this interesting phenomenon is a matter of dispute. It presents sufficiently distinctive features to be regarded as a clinical entity which offers puzzling problems to both the toxicologist and the allergist. To the syphilol-

ogist, its immediate practical importance lies in the safety of continuing arsenical therapy. In an effort to gain some hints as to the future tolerance of patients who have had this reaction, the authors reviewed the 11 cases that have occurred in the wards of Bellevue Hospital during the past 2 years. These cases represent about 3 percent of all the patients treated for the first time with arsenical drugs.

The authors' conclusions from this study are as follows: Early acute arsenical erythema is a clinical entity which should be differentiated from the later edematous exfoliative dermatitis. The mechanism of this reaction is unknown but it may be a response of the autonomic nervous system to arsenic. Neither the dose nor the type of trivalent arsenic nor the mode of injection seems to influence the reaction, and the spacing of treatments has no appreciable effect on its occurrence. Neither blood counts nor tests of hepatic function give any definite clues as to the nature of the reaction. Proof of the existence of antibodies by passive transfer is lacking. In uncomplicated early erythema subsequent therapy is not always well tolerated but the difficulties can usually be overcome. There are no definite criteria for determining in advance which patients will have nitritoid or gastrointestinal reactions to further treatment; intradermal and patch tests are useless for this purpose.

The authors find it advisable to stop treatment with arsenic during the early erythema and not to resume it until all signs of the reaction have disappeared. When the arsenical therapy is again instituted, the dose should be reduced and increased according to the patient's tolerance.

Chancres of the cervix. Irving S. Schipper. Illinois M. J., Oak Park. May 1939, 75: 457.

Every cervical lesion should be looked upon with suspicion of syphilis, especially erosions of the cervical lips which are solitary and whose margins do not invade the external os. Because of its rel-

atively inaccessible character the woman patient seldom appears in the physician's office with a symptomless cervical lesion. Women, however, are becoming more "cancer conscious" and are seeking periodic genital check-ups. One of the first symptoms is bleeding or spotting, for in a large ulcerated area the denuded surface may bleed quite freely. A cauliflower-like growth bordering on an ulcerated area is not always a carcinoma; a cervical chancre should be ruled out. During the early chancre stage, the blood Kahn and Wassermann reactions may be negative, and a diagnosis of syphilis must be made through the dark-field examination.

Early diagnosis of chancre of the cervix will save many women from reaching middle life as helpless cripples from syphilitic tabes.

Osteitis in early syphilis. Report of a case. John Brainard Squires and Alfred L. Weiner. Arch. Dermat. Syph., Chicago. May 1939, 39: 830.

The authors feel that the scarcity of actual reports of the occurrence of osteitis and periostitis in early syphilis warrants the presentation of this case. The case recently reported by Newman and Saunders is probably the first case of clear-cut osteitis in early syphilis to be recorded in the English literature. More such cases would be recognized if routine roentgenograms were obtained especially of patients complaining of headaches.

The patient, a white woman aged 29, was admitted to the Cincinnati General Hospital, complaining of headaches and a rash. Dark-field examination revealed *Spirochaeta pallida*, and the Kahn reaction of the blood was positive. Roentgenograms of the skull showed several fairly well circumscribed areas of bone destruction but those of other bone areas were negative. The patient's husband was found to have early syphilis, but their child, 3 years old, gave a negative reaction to the Kahn test of the blood. The patient's blood had been negative at the time of the child's birth. S.

had been separated from her husband for some time and had returned to him only 3 months prior to admission. After receiving 0.4 gm. of arsphenamine the patient had a definite cutaneous Herxheimer reaction and increased cephalalgia. She was then given 2 grains of bismuth subsalicylate in olive oil and several days later 0.4 gm. of arsphenamine, and the rash faded within 10 days. Antisymphilitic treatment was continued. Ten months after admission roentgenograms showed the skull as essentially normal, and the patient no longer had headaches.

Extensive fistula of the dorsum of the penis secondary to nodular lymphangitis caused by the virus of Nicolas and Favre's disease. Alberto Midana. *Dermosifilografo*, Torino. Dec. 1938, 13: 653.

A case is described in a man of 47 who had had a soft chancre about a year before complicated by inguinal adenitis. The breaking down of the inguinal buboes was followed by the development of a nodule on the dorsum of the penis which in turn broke down. A very extensive fistulous tract developed with many sacs. It lay along the dorsal surface of the penis between the skin and the corpora cavernosa and extended up to the root of the penis and the margin of the pubic arch.

Liquid from the fistulous tract proved to be an effective antigen for the Frei test showing that the condition was lymphogranulomatous in nature.

The lesion on the dorsum of the penis was a nodular lymphangitis caused by paradenitis. The case shows that the virus of this disease like that of soft chancre may cause inflammation of the lymphatic tracts and produce very long and complicated fistulas.

A case of acute arsenobenzol purpura and stomatorrhagia. Luigi Coricciati. *Dermosifilografo*, Torino. Nov. 1938, 13: 664.

A carpenter, 65 years of age, had contracted syphilis 30 years ago. He first came to the author Jan. 30, 1937 with

leukoplakia of the tongue, tertiary lesions on the limbs, slight generalized enlargement of the glands, sluggish patellar and eye reflexes, and an aortitis that was apparently syphilitic in nature—Wassermann, Meinicke, and Kahn reactions four plus. On Feb. 5, arsenobenzol treatment was begun alternating with bismuth, and up to May 1, 5.25 gm. arsenic and 2 gm. bismuth had been given. There was some improvement in the symptoms and the patient disappeared from view. He reappeared 6 months later, Nov. 15, during which time he had taken no treatment. Serum reaction before reactivation was four plus. Novarsenobenzol treatment was begun again associated with intravenous injections of mercuric which had to be given up after the second one because of bloody diarrhea. Iodide given intravenously was substituted and treatment continued until Feb. 10, 1938 when he had had 5.25 gm. arsenic and 10 intravenous injections of iodide. The patient disappeared again and did not return until June 15. Serum reaction before reactivation was four plus. Novarsenobenzol was given associated with iodobismuthate of quinine. In this series of treatments the novarsenobenzol was given in solution with 25 units hepatoamine. On the fourth injection of 0.60 gm. novarsenobenzol (first had been 0.15 gm.) the patient had exhaustion and fever for 6 hours but after that was able to resume his work. A week later another dose of 0.60 gm. arsenobenzol dissolved in 50 units hepatoamine was given. An hour after the injection he had chills, fever and paresthesia of the hands and feet. After another hour he had a copious hemorrhage from the mouth. Hemostatic injections were given and the hemorrhage decreased but continued to a certain degree until the next day. The next day there were hemorrhagic spots on the vault of the palate and scattered over the surface of the body. This was associated with slight pruritus. The hemorrhagic spots disappeared after a few days leaving a diffuse erythrocytosis of both legs due to an intense

secondary post-hemorrhagic anemia. Wassermann, Kahn, and Meinicke reactions were three plus.

Purpura after the administration of arsenobenzol is rather rare. There is evidently a reactive change in the walls of the vessels during the treatment until finally manifest hemorrhage takes place. This reactive change may persist indefinitely. But in the above case as the hemorrhage appeared during a third series of injections after two had been tolerated perfectly it must have been an allergic reaction, and the arsenobenzols must be antigens, that is, bodies capable of producing antibodies. There is a certain relationship between this phenomenon and that of Schwartzman in which there is an intense hemorrhagic reaction at the point on the skin where a bacterial filtrate is injected.

Aneurysm of the aorta with compression of the spinal cord; two case reports and review of literature. Michael B. Shimkin. *Ann. Int. Med.*, Lancaster. Apr. 1939, 12: 1709.

Shimkin reports two cases of syphilitic aneurysm of the aorta with erosion of the vertebrae and compression of the spinal cord. The 15-year survival of the first patient and the unilateral cord compression manifestations in the second patient are unusual.

Case 1. This patient, a 35-year-old Negro ship-worker has been under observation in the John Sealy Hospital clinic since 1921. Wassermann reactions in 1922 were positive, and he is believed to have received 8 intravenous and 16 buttock injections at this time. Roentgenographic studies in 1937 indicated a massive aneurysm of the transverse and descending portions of the aortic arch and extensive erosion of vertebrae on the left side. At present, the man is capable of some activity and his morale is excellent.

Case 2. A 54-year-old white night watchman was admitted to the hospital October 5, 1935, complaining of severe pain in the chest, pain in the low back, and difficulty of urination. There was

visible pulsation on the left side and erosion of the vertebrae was shown on roentgenogram. His course in the hospital was steadily downhill, and he expired on December 14, 1935. Autopsy showed that erosion of the vertebrae had produced direct pressure on the cord at the level of the sixth to eighth thoracic vertebrae.

In a general discussion, Shimkin says that all of the aneurysms of the aorta producing spinal cord compression reported in the literature are of syphilitic origin. This involvement of the cord is rare, however; of 170 aneurysms treated at the hospital only one (the reported case) involved the cord. He discusses the clinical and pathologic findings and the treatment and prognosis of 46 recorded cases.

Studies on the pathogenesis of syphilitic and tonic pupillary disturbances.

II. Romberg. *Arch. f. Psychiat., Berlin*. Apr. 15, 1939, 109: 785.

A series of studies was made for the purpose of establishing a differential diagnosis between Adie's syndrome and the pupillary changes due to syphilis which occur in tabes. Investigations were carried out on 84 nonamaurotic tabetics and taboparetics all of whom were past middle age. In 67 of these the serologic reactions for syphilis were positive in at least one of the body fluids. In the other 17 there was either a history of syphilis or there was no question, on the basis of clinical findings, in regard to the diagnosis of tabes or taboparesis. Patients who did not have partial or complete absence of tendon or periosteal reflexes were excluded, so that the findings approximated as closely as possible those of Adie's syndrome. Haab's pupillometer was used for the determination of the width of the pupil. Anisocoria was found to be present in 23 of the patients and mydriasis in 50 instances, the mydriasis being present unilaterally in 11 and bilaterally in 39 of the patients. Eight of the latter also had anisocoria. Practically all of the patients had some degree of irregularity of the pupils. Very little

variation in the diameter of the pupils was found in 25 patients who were observed for a period of weeks to months. This is an important differential point between the Adie and the tabetic pupil. The reaction to light was present to a greater or less degree in one or both pupils in 43 cases. In 12 out of 37 patients whose pupils did not react to light a definite reaction could be obtained by means of the Jupiter lamp. In all cases the degree of reaction was found to be independent of the size of the pupil. In 15 cases there was unilateral or bilateral absence of the reaction to accommodation. The lid-closing phenomenon was elicited by electrical stimulation of the orbicularis muscle. With the contraction of the orbicularis there is also a contraction of the pupil. This test which was carried out in 32 patients was positive unilaterally or bilaterally in 22 patients but only in those with large pupils. In 10 of these patients the reaction to accommodation was negative bilaterally. Absence of all reaction was found in 3 cases. In 35 patients the light reflex was tested after subcutaneous injection of 1 cc. of a 1 percent strychnine nitrate solution. It was found to be more prompt or more marked in 9 cases. Since in the Adie pupil there is always an increased pupillary reaction, this test is not of great importance in the differential diagnosis. One drop of each of 1 percent solutions of pilocarpine, homatropine, cocaine, and adrenalin was applied to the conjunctivae of 25 patients. Following the application of pilocarpine the pupil became myotic after an interval of 30 minutes. The larger the pupil was, the greater the reaction to the drug. This increased pharmacologic irritability of the sphincter in tabes has also been observed by Peyret. Following the application of homatropine the pupil increased in size by about 5 mm. after 30 to 60 minutes. After cocaine the increase in pupillary size never exceeded 3.5 mm. This amount of dilatation occurred within 15 to 30 minutes. Adrenalin produced a dilatation which did not exceed 1 mm. which comes within the mar-

gin of error in determining the size of the pupil. The author concludes that pharmacologic reactions are not suitable in the differentiation between the tabetic and Adie pupil, since the time factor is the same for the tabetic as for the normal pupil, whereas the Adie pupil reacts much more quickly. Further experiments with these patients showed that there is a relationship between pupillary size and muscle tonus, pupillary size and sweat secretion, and possibly between pupillary size and bladder function. There was found to be no relationship between the pupillary findings and circulatory disturbances.

A syndrome simulating tabes dorsalis.

Maurice J. Costello. New York State J. Med., New York. Apr. 15, 1939, 39: 781.

A knowledge of Adie's syndrome, also known as the pseudosyphilitic or the nonsyphilitic Argyll Robertson pupil, is of great importance to the physician diagnosing and treating syphilis. It is frequently mistaken for the true Argyll Robertson pupil and this leads to serious errors in management and treatment of the patient. During the past 10 years, Costello has seen this pupillary abnormality in a number of patients who were not infected with syphilis and recently in a patient with syphilis.

Some points of dissimilarity between the false Argyll Robertson pupil and the Argyll Robertson pupil of tabes dorsalis are: In the former condition 80 percent of the cases are in women; it is unilateral and in 80 percent of the cases occurs on the left side only; the pupil is somewhat dilated and round; the inequality between pupils is striking; the pupil contracts slowly to accommodation, remains stationary for many seconds, then dilates sluggishly; it dilates rapidly and completely to mydriatics; there is generally a history of severe shock and emotional instability. In the true Argyll Robertson pupil both sexes are affected, and the condition occurs bilaterally in the majority of cases; the pupil is contracted; inequality between

pupils, if present, escapes notice because of the small size of pupil and bilateralism; pupil contracts promptly to accommodation and assumes original size immediately after; it dilates slowly and imperfectly to mydriatics; there is a history of syphilis, and in 90 percent of cases it is an almost infallible sign of tabes dorsalis.

Acquired syphilis of the colon. V. Faber. Virchow's Arch. f. path. Anat., Berlin. Mar. 17, 1939, 303: 406.

A diagnosis of syphilis of the colon was made in a 69-year-old laborer who died of chronic myocarditis 9 days after entering the hospital. At the time of admission he was markedly emaciated, had râles over both lung areas, a systolic murmur over the base of the heart, and an irregular pulse. The liver was enlarged and the left leg and foot were edematous. The Wassermann and Sachs-Georgi reactions were negative. The autopsy findings were brown atrophy and cloudy swelling of the heart muscle and senile atrophy of the "internal organs." In the colon, mucosal defects of varying size were found (from a penny to a fifty cent piece), with glistening bases and grayish-red borders. No tubercles were found either in the mucosa or the peritoneum. The mesenteric lymph nodes were pea-sized to bean-sized, and "had normal blood content." Histologic section showed that most of the lesions extended to the muscularis mucosae. The entire wall of the colon contained areas of granulation tissue containing chiefly "lymphoid" and plasma cells but also epithelioid cells and fibroblasts. The blood vessels showed varying degrees of endangiitis from barely perceptible changes to complete occlusion of the lumen. The veins showed the greatest changes, many of them having almost complete dissolution of the elastic fibers. The author states that he feels justified in making a diagnosis of syphilis of the colon in spite of the fact that syphilitic changes could be demonstrated nowhere else in the body.

DIAGNOSIS

Systematic study of the variability of the gonococcus in its most common localizations. Luigi Semmola. Dermosiflografo, Milano. Dec. 1938, 13: 691.

The author made a careful study of the gonococci from 70 cases of gonorrhea, 31 in men, 31 in women, and 8 in children. They were followed from the beginning through the various complications and different stages of treatment until cure, and the biologic characteristics of the gonococci and the accompanying diplococci were studied carefully.

He found that throughout these processes the gonococcus always keeps its characteristic morphology and staining properties. The colonies also preserve their characteristic form and appearance through many transplantations, and the first transplantations keep their characteristic staining properties which are so useful in diagnosis. The gonococci isolated from lesions may show variation in their sugar-fermenting reactions. It is true that gonococci in vitro and under the influence of certain stimulating factors may show changes in morphology and staining properties, but this does not alter the fact that they are constant in vivo.

The various forms of diplococci which appear in gonorrheal lesions after the disappearance of the gonococci are no variants of gonococci at all but entirely distinct forms.

The second stage of the agglutination reaction. Alexander S. Wiener and Morris Herman. J. Immunol., Baltimore. Apr. 1939, 36: 255.

The common conception of precipitative and agglutinative reactions is that they proceed in two separate stages: (1) A specific combination between the antigen and its antibody, and (2)

nonspecific stage of aggregation of the sensitized particles in which electrolytes are factors. Marrack has recently offered another interpretation. He believes that molecules or particles of antigen and antibody molecules alternately combine to build up a three-dimensional lattice or mosaic because of the presence in the antigenic particles and antibody molecules of several combining groups. According to this concept, combination of antigen and antibody and aggregation occur simultaneously, and both "stages" would be specific.

The authors have made numerous experiments with syphilitic serums containing iso-agglutinins, tested against mixtures of Kline antigen and human red blood cells. In all these experiments the agglutinative reactions were invariably specific whether the clumping of the red cells proceeded at a rate greater, less, or equal to that of the Kline antigen. For example, in tests made with a group A syphilitic serum against mixtures of group B cells and Kline antigen, the clumps consisted either entirely of the latter mixture or of red blood cells, never both, as could be demonstrated by examining the preparations under the low power of the microscope. To the naked eye the two sorts of clumps were readily distinguishable by their colors, either red or white. The aggregations were likewise specific in similar tests made with mixtures of syphilitic serums and anti-M testing fluids and emulsions of Kline antigen and human blood of group O, type M. On the other hand, when mixtures of Kline antigen and human red cells were treated with high dilutions of ferric chloride solution in saline solution, heterogeneous clumps resulted. In the latter instance, all the clumps appeared alike to the naked eye, the color being a pale red.

The authors discuss the work of Topley, Wilson, Duncan, Abramson, Hooker, and Boyd in research on agglutination. They also discuss the agglutination resulting from mixtures of human red blood cells and typhoid bacilli, human

red cells and pneumococci (types I and XIV), and chicken red cells and human red cells.

The occurrence of mixed agglutination as shown by Hooker and Boyd, Abramson, and others cannot be denied; but the fact that specific agglutination is more common is a strong argument for Marrack's assumption of specific forces influencing aggregation. The present findings indicate that when antibody is in excess, nonspecific clumping may occur; otherwise the tendency is for cells of the same sort to stick together. Similar conclusions were reached by Duncan in 1938 in a study on the rate of grossly visible aggregation in mixed agglutinative systems.

Positive Wassermann reaction in spirochetal infections other than syphilis.

Report of a case. Thomas W. Murrell. Arch. Dermat. & Syph., Chicago. Apr. 1939, 39:667.

In many of the States laws have been passed, or are in the making, by which a negative Wassermann reaction is a prerequisite to matrimony. Since, however, the existence of an occasional false positive reaction is an accepted fact, many disagreeable situations are in the making, the author says. Five more or less commonly seen entities are accepted as due to spirilliform infection—syphilis, yaws, relapsing fever, rat bite fever, and Vincent's angina and with the first three a positive Wassermann reaction is to be expected. Murrell reports a case of relapsing fever in which it was felt that syphilis could be ruled out since a positive serologic reaction disappeared under treatment, and the infection was due to *Spirochaeta novyi*.

The patient was a boy of 7 years who had marked lassitude, swelling of cervical glands, and several brief phases of slight fever. His Negro nurse had had a positive Wassermann reaction 2 years previously but had been under treatment. The child had not been bitten by a rat, but had been bitten by a cat and also by fleas and mosquitoes. A scratched area

on the thigh had been very slow in healing. The Wassermann reaction was positive with both antigens and Kahn and Kline tests were also positive. These tests were checked by two other laboratories. Wassermann tests on the immediate family were all negative. A bacteriologist identified *Spirochaeta novyi*, one of several described as the cause of relapsing fever. The child was treated with mapharsen, and after the fourth and final injection 3 laboratories reported the blood as negative to the Wassermann, Kline, and Kahn tests. Six months later the blood was still reported as negative.

Temporarily positive Kahn and Wassermann reactions in infectious mononucleosis: Report of a case. Joseph F. Sadusk, Jr. J. A. M. A., Chicago. Apr. 29, 1939, 112:1682.

That temporarily positive serologic tests for syphilis may occur in infectious mononucleosis without evidence of syphilis is not generally recognized, and the author reports a case. A student nurse was admitted on January 10 to the New Haven Hospital with a diagnosis of German measles. She had a cutaneous eruption over neck, chest, and abdomen, and enlargement of cervical nodes but was not uncomfortably ill. The leukocyte count showed a number of large cells characteristic of those ordinarily present in infectious mononucleosis. The sheep cell agglutination test was positive in a dilution of 1:512, the Kahn reaction was 4 plus and the Wasserman reaction negative with the alcoholic antigen but 4 plus with the cholesterinized antigen. On January 15 the sheep cell agglutination test was positive in a dilution of 1:4,096, and the Kahn and the cholesterinized Wasserman reactions were positive. These reactions remained positive until February 19. Whether the high titer for heterophile antibodies of 1:4,096 has any relation to the false positive Wassermann reactions is not clear, the author says. The heterophile antigens persisted in high dilution (1:256) even after the serologic reactions for

syphilis became negative in the tenth week.

No adequate explanation has been advanced for the cause or nature of these false positive reactions. Partial removal of heterophile antibodies has no effect on the tests for syphilis nor do the sheep cell titers necessarily parallel these tests.

In the past 17 years there have been 46 admissions to this hospital with a diagnosis of infectious mononucleosis. In 37, either Kahn or Wassermann tests were done, and 3 (about 8 percent) yielded positive results. More patients with positive reactions for syphilis might have been found if blood tests had been repeated on more cases during the subsequent course of their illness.

The Laughlen test for syphilis. Sumner Price. New York State J. Med., New York. May 1, 1939, 39:880.

Price reports on a series of 1,496 cases, in which Wassermann (Kolmer modification), Kahn, and Laughlen tests were done on each serum. In 60 cases that showed anticomplementary Wassermann reactions both Kahn and Laughlen tests were completed with satisfactory readings. In 1,339 there was complete agreement in all tests, and in 97 there was a variable degree of disagreement. The Kahn and Laughlen tests agreed with each other more closely than with the Wassermann since the Laughlen reagent is prepared through a modification of the Kahn antigen. Price found that these tests were better than the Wassermann in "picking up" a treated case of syphilis, which recommends them for use for prospective blood donors where it is advisable to discard treated as well as untreated cases of syphilis. The Kahn and Laughlen tests were less subject to fluctuations under treatment since they remained positive in a low degree for a variable but long period after the Wassermann became negative. He recommends the Laughlen test for use on babies or whenever the amount of serum available is small.

Price emphasizes that in reading the result the size of the clumps is not a

side to the positiveness of the Laughlen test, but the time element, i. e., the time required for agglutination to become visible, is the guide. Readings are best made with the slide held above a dark background. Readings made through the microscope will lead to errors in interpretation.

In an appendix to this article, Price discusses certain criticisms of the Laughlen test which were brought out at a conference between Rein, Mahoney, Coca, a representative of the Lederle Company, and himself. With some of these criticisms he agrees and for others he advances arguments in favor of the test. He believes that the Laughlen reagent warrants further investigation and use.

TREATMENT

Gonococcal proctitis treated with M & B 693. Edward T. Renbom. *Brit. M. J.*, London. Apr. 8, 1939, 2: 749.

In a letter to the editor, the author reports the result of treatment with M & B 693 in a case of gonococcal proctitis. Three days after having rectal intercourse the patient began to suffer from pain and tenesmus, and he passed mucus and pus. Digital examination of the rectum 10 days after the homosexual intercourse was painful, the sphincter being in spasm. A proctoscopic examination revealed an area of yellow mucus on the posterior rectal wall about 2 inches within the anal margin and beneath this was a round shallow ulcer three-quarters of an inch in diameter. This ulcer was intensely inflamed but there was no bleeding. Examination of the pus and smears from the ulcer showed large numbers of gonococci.

The patient was given M & B 693, 6 tablets (3 grams) a day for 4 days, followed by 4 tablets (2 grams) a day for 3 days, and then 2 tablets (1 gram) a day for 7 more days. No local treatment was given. After a week of treatment with the drug, gonococcal vaccine

was given and continued for a month. Improvement began within one day after treatment with M & B 693 was started. Three days later the ulcer was bleeding freely, and the pain and tenderness had almost disappeared. In a further three days the ulcer had healed, the pain had completely gone, and defecation was not difficult. Examination of smears from the site of the ulcer revealed no gonococci.

Criteria of cure included a gonococcal complement fixation test and a provocative injection of 750 million gonococci. No gonococci were found in rectal smears 2 months after treatment with M & B 693 had been discontinued.

The drug produced no toxic symptoms.

Varioliform eruption from sulfanilamide.

D. E. H. Cleveland. *Arch. Dermat. & Syph.*, Chicago. Apr. 1939, 39: 693.

An East Indian coolie was admitted to the Vancouver General Hospital complaining of headache, nausea, vomiting, and a rash on the face and arms for 2 days.

Variola was suspected and the patient was sent to the isolation department. No history of any value could be obtained, and he said he had taken no medicine. There was moderate edema of the entire face, and on the skin of the face, neck, arms, and hands were numerous pustules, discrete and nowhere confluent. On the trunk the lesions were of the same uniformly pustular character. There were no macules, papules, or vesicles. There was no complaint or evidence of itching. By accident it was learned that the patient had been attending a clinic for acute gonorrhea and had been instructed to take the usual dosage of sulfanilamide and that he had taken 600 grains by mouth in 9 days. None had been taken in the hospital. The temperature was normal after the fourth day in the hospital. There was a slight infiltration and pigmentation still observed 2 weeks later. A peculiar aroma, resembling pineapples, on the patient's breath was noticed by several attendants.

While it was not proved definitely that this eruption was due to sulfanilamide the writer believes that it was the expression of hypersensitivity to that drug and of a morphologic character not hitherto described in this connection.

The role of the treatment of syphilis in the prevention of cardiovascular involvement. William Paul Thompson, Wilfred J. Comeau and Paul D. White. *Am. Heart J.*, St. Louis. Mar. 1939, 17:281.

Records of persons who had contracted syphilis 15 to 25 years previous to this study were taken from the files of the Massachusetts General Hospital and the Boston Dispensary and 260 patients were followed up and reexamined. These data have been analyzed in detail with respect to the present cardiovascular status of the patients and the relationship of treatment thereto.

Of this group, 19 persons had heart disease of other than syphilitic origin and were eliminated from the analysis. Of the remaining 241 patients, 18 (7 percent) had definite cardiovascular syphilis and 8 (3 percent) had probable aortitis. This figure (10 percent) agrees with that other observers have found for the incidence of cardiovascular syphilis.

The analysis shows very little difference in the amount of treatment received by the patients who now have normal aortas, questionable aortitis, and probable aortitis, but the 18 patients with definite cardiovascular syphilis without exception had received less than 20 arsenic and 20 bismuth or mercury injections during the first 5 years following their infection. Only one patient in each group of those who now have probable or definite cardiovascular syphilis received late treatment (6 to 15 years after infection) approaching an adequate amount.

The authors feel that this study gives some support to their clinical impression that adequate treatment of syphilis tends to prevent the later clinical manifestations of cardiovascular syphilis. They feel, however, that more years must

elapse before it will be possible to follow up the late results (15 to 25 years after infection) of the adequate early treatment of syphilis.

Sulfanilamide in medicine. R. O. Russell. *J. M. A. Alabama, Montgomery.* Apr. 1939, 8:348.

The mode of action of sulfanilamide is still uncertain. The question of whether the action of the drug is bacteriostatic, bactericidal, or both, is unanswered. There is also a controversy as to whether the drug causes an increase in phagocytosis. Several observers have shown that sulfanilamide in man is excreted almost entirely by the kidneys either in the free or the conjugated form. Pinto has shown that the concentration of sulfanilamide in human milk followed a course similar to that found by other workers for its concentration in blood. The period of concentration in milk, however, seemed to lag behind that in the blood by several hours. A blood level of from 8 to 12 mg. of sulfanilamide per 100 cc. should be obtained to get the desired therapeutic effect. The excretion of sulfanilamide is diminished in disturbed kidney function.

After ingestion of sulfanilamide the symptoms that may be noted are headache, dizziness, nervousness, dyspnea, cyanosis, nausea, confusion, general malaise, weakness, general intestinal disturbance, a sensation similar to alcohol intoxication, and sensory disturbance of the toes (tingling and sensitiveness). A person should not operate a plane or drive a motor vehicle while taking the drug. Ambulatory patients cannot tolerate as large doses as bed patients.

More serious toxic effects are methemoglobinemia, sulfhemoglobinemia, skin rash, optic neuritis, peripheral neuritis, toxic hepatitis, agranulocytosis, and acute hemolytic anemia. The skin eruptions reported have ranged from maculopapular lesions over the body to severe exfoliative dermatitis and purpura. A rise in temperature is often seen after taking sulfanilamide but rapidly becomes normal when the medicine

on is stopped. Agranulocytosis has been reported. In many of these patients the leukocyte count has fallen to very low levels with complete disappearance of the neutrophils. In some patients a stimulation of the leukocytes has occurred, the counts going to extremely high levels (25,000 to 75,000) after taking the drug. Several cases of acute hemolytic anemia have developed. This has been treated by discontinuing the sulfanilamide, forcing fluids, and giving blood transfusions. It is thought that the patients in whom agranulocytosis or acute hemolytic anemia have developed may be allergic to or have an idiosyncrasy toward sulfanilamide.

It is essential that all patients taking the drug should be examined carefully at frequent intervals and that they should have blood counts made often during the course of treatment. Sulfanilamide is an excellent drug, but it is dangerous when used indiscriminately.

Over-treatment in syphilis. Frank E. Cormia. *Canad. M. A. J.*, Montreal. May 1939, 40:445.

During the past few years Cormia says he has observed several examples of a well defined over-treatment syndrome occurring in patients receiving combined neoarsphenamine and bismuth which, although well known to syphilologists, has not received recognition in the literature. This syndrome consists of symptoms referable to the nervous system as manifested by nervous irritability, insomnia, and headaches; to the gastrointestinal tract, as anorexia, chronic dyspepsia and constipation; to the respiratory system, as a chronic cough; and general weakness, malaise, and loss of weight. Cormia gives the details of 5 cases of over-treatment, 3 of which illustrate this syndrome, the fourth, lacking the syndrome, has manifestations of both bismuth and arsenical intolerance, and the fifth illustrates the influence of arsenical therapy in the production of some of the characteristic features.

Because of continued positive Wassermann reactions, and against the advice

of consultants to discontinue antisyphilitic treatment, the attending physicians continued their treatment of these patients although there was an increasing symptom-complex. In a comparatively short time after treatments were discontinued the symptoms disappeared in each case. Three of the 5 patients had inactive, latent syphilis. A fourth patient developed mucocutaneous relapse but was grossly over-treated with arsenic in relatively huge dosage, 0.9 gram for a frail woman weighing 98 pounds. The fifth patient had central nervous system involvement of the parietic type which did not, of course, respond to standard antisyphilitic treatment.

Cormia feels that these cases exemplify the current medical trend of under-examination and over-treatment of the patient with syphilis. In latent syphilis particularly is the fetish of treatment carried to undesirable lengths, he says. Until the practising physician makes a thorough initial investigation of every patient with a syphilitic infection before treatment is begun, until he asks himself what lies back of the positive Wassermann and makes a creditable attempt to differentiate late, inactive latency from active visceral syphilis, such tragedies will continue to occur.

Death from granulocytopenia after sulfanilamide therapy. Philip Corr and Ralph N. Root. *J. A. M. A.*, Chicago. May 13, 1939, 112:1939.

The patient, a white woman, aged 22, entered the Riverside County Hospital because of a severe throat infection of about two weeks' duration. After examination the condition was recognized as agranulocytic angina, and the patient died on the third hospital day. After repeated questioning she admitted, on the day of her death, that she had taken tablets for leukorrhea, and investigation revealed that she had taken 540 grains (35 gm.) of sulfanilamide in a period of 15 days, under the direction of an osteopathic physician. The final diagnosis was agranulocytic angina caused

presumably by sulfanilamide. There was serologic evidence of syphilis.

Nine deaths, according to a compilation by Kraeke in Oct. 1938, have previously been recorded in the literature from agranulocytosis apparently caused by sulfanilamide. For the prevention of this catastrophe suggestions have been made of having repeated frequent blood counts on patients under treatment with the drug, of withdrawing the drug when there are toxic symptoms, and of watching the patient very closely during treatment. The authors add a third point in prevention, and that is, the dosage. After studying the dosage reported in these fatal cases, they believe that the general practitioner may safely give up to 20 gm. of sulfanilamide before being concerned about agranulocytosis, and this dosage may well care for many of the simpler infections treated with this drug.

Treatment of vulvovaginitis with estrogen. Charles Mazer and Fred R. Shechter. J. A. M. A., Chicago, May 13, 1939, 112:1925.

The basis of treatment of vulvovaginitis with estrogen is the ability of the substance to create a temporary maturity environment in the vagina of the child and thus render it resistant to pathogenic bacteria. The dose of estrogen must be sufficient to cornify the vaginal epithelium and to reduce the pH of the vaginal secretions to a point below 6. Treatment for 8 weeks, despite an earlier clinical and bacteriologic cure, is a safeguard against recurrence of the infection. In employing a new product in the treatment of human ailments, its safety must be established first. The authors give the following in defense of the use of estrogen: (1) Rats and monkeys given considerable quantities of estrogen become estrous and reproduce normally. (2) The blood of the unborn infant is normally surcharged with estrogen to a degree far greater than that of children treated with the maximum doses of the substance. (3) A few treated children who have already attained puberty

have menstruated at the predicted age. (4) Regularly menstruating women who have received estrogen menstruated normally after withdrawal of the treatment and have borne normal offspring.

The authors report on 118 children from 18 months to 11 years of age, who were reported at the Philadelphia General Hospital from 1935 to 1937 for treatment of gonococcal vulvovaginitis. Of the 118 children 81 were treated by means of hypodermic injections of estradiol benzoate (progynon-B); 34 received the same product as vaginal suppositories and 3 were given estradiol (progynon-DH) orally. The hypodermic injections produced a clinical and bacteriologic cure in 78 of 81 children, with a 10 per cent incidence of recurrence. The recurrences were more numerous and earlier where there was a shorter course of treatment, suggesting that incomplete cure was the cause. Treatment with vaginal suppositories produced a clinical and bacteriologic cure in 33 of the children so treated, without any recurrence in the 26 who were observed for a relatively long time. Oral treatment was ineffective in the 3 children who received as much as 1,500 rat units daily for 6 weeks.

Side effects, such as growth of pubic hair, uterine bleeding and enlargement of the breasts, were temporary and were more frequently encountered with hypodermic than with local treatment with estrogen.

The reaction of gonococci to chemotherapy. Felke. Klin. Wchnschr., Berlin, Apr. 22, 1939, 18:568.

It is the author's opinion that cases of gonorrhea which after apparent successful chemotherapy again show gonococci are not to be classified as failures, but that the only real failures are those which do not respond at all to this type of treatment. Based on the reaction of gonococci (obtained from 140 patients) to diseptal C which had been added to the culture medium, he believes that the ability to resist the action of the drug

uries with different strains of gonococci. He has differentiated 3 types of gonococci according to their ability to grow in the presence of disethyl C. In type I growth is inhibited by 0.5 mg. percent, in type II by 1.0 mg. percent, and in type III growth is not inhibited by 1.0 mg. percent and sometimes not even by 2.0 mg. percent. He found that with con-

tinued unsuccessful chemotherapy the resistance of gonococci to the drug increased. Type III strains were found almost entirely in treated cases. Short courses of treatment were found to be more successful than long-continued treatment. More cures were obtained when chemotherapy was delayed for 10 days after the onset of the disease.



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Issued by the United States Public Health Service for use in its cooperative work with the State and local Health Departments and the physician in private practice.

UNITED STATES PUBLIC HEALTH SERVICE

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The Outlook for Syphilis Control

LOUISE PEARCE, M. D., Princeton, N. J.

The title, "The Outlook for Syphilis Control," suggests something of the nature of a prophecy, and a prophetic role is one that a scientist should be extremely chary in assuming (especially so in the present instance since the subject is syphilis). All who are familiar with this disease would agree that on this subject "a little learning is a dangerous thing." On the other hand, any prudent person, embarked on a new enterprise, does well to pause every now and then in order to take account of stock. He adds up both sides of the ledger and hopes that his trial balance comes out in black, not in red, figures. He tries to be wise before and not after the event, and in his survey of the situation he is more concerned with unfavorable than with favorable results. If he is a true pioneer, he will not allow himself to become pessimistic over the discouraging features of his enterprise, but the rosy hues of his accomplished successes will not blind him to the grey pitfalls of past failures which might be his ultimate undoing. He is a pessimistic optimist.

It is in a spirit of survey and of contemplation, if I may use the word, that I shall consider today some of the points concerned in our present outlook for syphilis control in this country. You are, of course, familiar with the great mass of statistical and other objective information relating to syphilis which has been assiduously brought together during the past few years. This information is one of the prime essentials of our equipment

for waging a successful campaign, and such knowledge and the conclusions to be drawn therefrom must enter into any comprehensive survey of the outlook for syphilis control. Today, however, I shall put aside this highly essential aspect of the subject in favor of certain other important considerations which are not so frequently discussed. I shall begin with the credit side of the ledger.

The first item, and perhaps the most significant of all our assets, is the sound attitude towards the whole question of health which the people of this country are beginning to take. More and more it is becoming the general, the prevalent point of view that good health is not necessarily just a matter of luck, a fortunate combination of good inheritance and favorable environment, together with the bare requisite of public health measures and together also with the minimum of hospital or other institutional care. Opposed to this rather negative point of view of passive acceptance or receptivity is a gradually growing positive attitude of active interest and concern. The public is aware as never before of the desirability of individual and community good health, and, in addition, is increasingly aware of what can be done in this direction by individual and concerted action. Furthermore, the time is coming, if it is not already here, when the means to attain the desired end are generally taken for granted. In other words, people are not merely hoping for good health, they are considering it an essential for life, and in consequence thereof the means to assure it are being looked upon in the nature of a right, not a privilege.

The result of this steadily growing point of view means an ever-increasing

NOTE.—From the Rockefeller Institute of Medical Research. Presented at the Annual Conference of Health Officers and Public Health Nurses, Saratoga Springs, New York, June 30, 1938.

service. It means more and probably larger health organizations of one kind or another which can devote themselves efficiently to additional problems of preventive and curative medicine. It means increasing amounts of both public and private medical care. In an enlarged scope of public health activity and of medical attention, syphilis will unquestionably occupy a prominent place. The length of time it will keep this position is not entirely unpredictable but if we are wise, we shall not let our hopes unduly influence our plans for a long and continuous campaign.

In any event, there can be no question that a genuine public interest and concern in matters of individual and community health is a proud asset of any people. From a general standpoint as well as the particular one we are considering today, no effort is too great to continue and to increase this interest.

My second credit item is education. Despite all the criticism of our educational institutions and technics, the fact remains that educational opportunities in this country are remarkable. More and more individuals are learning to read and write, more and more persons are acquiring more and more information. The elements for an education are, generally speaking, freely available. I am not here concerned with the question of whether the education acquired is wisely used by any or all of a community. I merely wish to point out that the success of an enterprise such as the present antisiphilis campaign is tremendously facilitated by the fact that widespread educational opportunities have been extensively used in this country for a considerable time.

I would also mention in connection with this matter of education, the unprecedented means for communication enjoyed by the people of this country. We have happily not yet deprived ourselves of a free press. And if reports be correct, our radio audiences represent a large proportion of our population. The diffusion of information is relatively easy.

The third credit item is the enormous available wealth of this country. I shall

not discuss this point in any detail, but I think it is essential to realize that a campaign such as the present one in a country as large and as populous as ours, must necessarily be a far flung venture. It must penetrate into all corners of town and country, it must reach all sorts and conditions of man and it must continue for a longer or shorter time. Such an ambitious enterprise can only be successfully prosecuted under conditions of adequate financial support. If the possibility for adequate financial support did not exist, there would be no point in even considering the undertaking.

The fourth credit item is represented by our knowledge of syphilis and of the various therapeutic agents and procedures with which the syphilitic patient may be satisfactorily treated. We owe a great body of information concerning the manifestations of the disease to astute clinical observation covering a period of four centuries. The efforts of investigators during the present century have resulted in the identification and isolation of the causative agent and in the elaboration of precise diagnostic methods. We are now well informed on many aspects of the pathogenesis of the disease and of the reaction of the body to the infection.

We may congratulate ourselves on our present knowledge concerning the treatment of syphilis. We have in our hands a much more satisfactory therapy than ever existed before. We possess certain recently elaborated drugs not dreamed of in the old mercury and guaiac days which have proved to be highly efficient therapeutic agents. And we now have precise information on the most advantageous methods of employing these drugs—the actual conduct of treatment. The treatment of a syphilitic patient today is no longer a “hit or miss” affair, compounded of as much mercury as the patient will stand together with any other drug or drugs that happen to be in vogue at the moment. On the contrary, it is a systematic procedure which has been logically developed from the detailed analyses of the results obtained in thousands of patients treated by modern methods. It

is perfectly true to say that our present knowledge endows us with a high degree of competency in the diagnosis of syphilis and further, that it enables us to treat the majority of syphilitic patients, and certainly the great majority of early cases, in a satisfactory manner.

These items on the credit side of our trial balance sheet by no means exhaust the list of our tangible and intangible assets. Others could profitably be discussed and, indeed, they deserve a thorough consideration in any comprehensive survey of the subject, but at present, the four I have mentioned will have to serve as indicators of our happily solvent condition. It goes without saying that any and all efforts to increase our assets should be universally supported; our campaign will need all that we can possibly provide.

I must now descend from the shining heights of acquired knowledge, of positive scientific accomplishment and of the encouragement and assistance afforded by public interest and concern, to the gloomy depths of the debit side of the ledger. Here again it is impossible to cover this aspect of the question at all adequately and I shall limit myself to the three items which seem to me of the greatest importance. They deserve our most serious consideration for in their many implications they adversely affect every aspect of our problem. It is surely the part of wisdom, first to recognize these liabilities, second, to limit them as efficiently as lies in our power and third, to endeavor to eradicate them as quickly and thoroughly as possible.

The first debit item I have called inheritance and education, for want of a better designation. The successful results of antisiphilis campaigns in Sweden, Denmark, and Great Britain have very naturally been held up to us as noteworthy examples of what it has been possible to accomplish. These enviable achievements at once provoke the feeling that what others can do, so can we. Certainly no one would be so foolish as to wish or to try to dissipate this feeling of emulation, but we should be lacking in critical discrimination if we did not real-

ize that the problem in this country is complicated by certain factors not present in these other countries. We must not delude ourselves as to the far-reaching influence which these factors are bound to exert against both an immediate and a remote success.

In the first place, our population is racially extremely heterogeneous, as compared with the relatively homogeneous population of the Scandinavian countries and England. Our various peoples have many different traditions and customs and different habits of thought and behavior. Their mental reactions to an educational matter, to a political proposition, to a proposed public health measure are not similar, let alone identical. What might be a successful procedure in upper New York State might be a complete failure among the southern Negroes. What could be followed among the Italian clinic patients in an Eastern city hospital might not be at all successful with the Scandinavian population of our Middle Western States.

It is perfectly obvious that to achieve the objective of syphilis control and prevention, a sense of responsibility and cooperation must be developed in two directions. The cooperation of the public generally is essential in order that individuals infected with syphilis be found. And second, each patient must have the requisite responsibility toward himself and others which is necessary for the initiation, continuation and completion of his treatment. Obviously, it is useless from the point of view of preventing the spread of syphilis, to bring the infected under treatment if they discontinue attendance before being rendered noninfectious. The long continuance of treatment is a vital necessity of our program. Can anyone suppose for one moment that a sense of responsibility in these respects will show itself to the same degree among different peoples which make up our population?

Still another great difference between this country and those of Scandinavia and Great Britain is size and distance. Our people are distributed over an enormous area with correspondingly long dis-

tances. These factors, of course, are of special importance with respect to caring for rural and semirural populations. It has been said that syphilis is no respecter of persons. It is equally true that syphilis does not discriminate between town and country. If we are to eradicate it, the problem presented by the various rural sections of the country is so incredibly difficult that one wonders how it can be solved.

There can be no diversity of opinion concerning the necessity of education in an antisiphilis campaign. There is, however, a considerable diversity of opinion on the precise aspects of the subject which should be emphasized as well as the methods to be employed in doing it. These are matters which should be thoughtfully considered and decided with all the wisdom we possess. I have been particularly concerned with the prevailing widespread impression that all that is necessary to do is to find every one who has a positive blood test and then institute treatment until the test is negative. This, in essence, is what a very large number of people now consider to be the sole objective of antisiphilis control. Any educational effort which results only in such a restricted point of view is certainly inadequate.

Together with the education of the public must come the education of the doctor. The average physician throughout the country is not particularly concerned with syphilis, and by and large, has had only a limited experience with modern methods of treatment. During the early days of the campaign he will assuredly take a few more specimens of blood for serologic tests and he may refer suspected cases to specialists or clinics and he himself may treat a few more cases than usual. As time goes on, however, it is certainly possible that his interest will become less and less, and in a few years, he will probably have minimized the necessity of continued interest or he may have no interest at all.

I have heard more than one authority state with conviction that at present the average physician does not know how to treat syphilis. If that is true, the situa-

tion has the most serious implications. A doctor told me the other day that he had recently heard the leading specialist of one state say that he, the specialist, does not ever see the development of any untoward effects or complications during the treatment of his syphilitic patients. My first thought was that the specialist was a specialist by courtesy only and that he could have only a very few patients. But I was entirely mistaken for he has a large number. The correct answer is that his treatment comprises such very small doses of drugs that an untoward effect would be extremely unlikely. Of course, the fact that a beneficial therapeutic effect would likewise be extremely unlikely is not appreciated by his patients.

I do not mean to imply by this story that this particular physician is typical of the profession throughout the country, but there is no question, I believe, that if the antisiphilis control campaign is to be completely successful, a special educational effort will have to be undertaken by the medical profession. This, I think, must take two forms. In the first place, the individual physician who plans to include in his practice the care of syphilitic patients will have to have special training to this end. In the second place, it will be necessary for members of the medical profession as a group to appreciate more particularly than has hitherto been the case the essential part they must play in this problem. The measure of success of syphilis control will depend largely upon the degree and persistence of interest in the matter held by the majority of physicians throughout the country.

My second debit item I have called administrative and executive. If the results of more or less extensive surveys are any indication of the true situation, during the next few years a very large number of people will be found in the United States who have a positive serologic test of one kind or another. What is going to be done about these individuals? Is every one of them to be treated? The affirmative answer of the laity is of course erroneous, but only the physician skilled by experience can decide which patient it is wise not to treat with the antisiphilitic

remedies now being talked about so liberally and so generally. It is at least debatable whether the average hospital clinic or the average physician throughout the country is in a position to treat syphilitic patients in an ideal manner. It must be remembered that the setup and conduct of a syphilis clinic differs in many important particulars from a clinic in which other diseases are handled. Furthermore, the present public and private facilities of the country are not yet equipped to handle the additional load of a large increase in the number of patients.

The question of enlarging our present facilities and of establishing additional ones is highly pertinent. Where are the properly trained medical staffs to be found? Should one attempt to set up special treatment centers in rural districts and in small towns? Or would it be more desirable to concentrate on the establishment of adequate facilities in the cities of a given rural area which would be properly spaced with respect to the surrounding country population and neighboring cities and towns? On the other hand, it may be that rural and semi-rural districts could best be served by the establishment of movable diagnostic and treatment centers in charge of well trained specialists with whom the local physician may consult and to whom he could send his syphilitic patients for treatment. A clinic on wheels is by no means an impossible solution of this difficult problem. One fact, however, stands out fairly clearly. In concentrated population centers there must be the requisite number of appropriately situated, properly equipped and adequately staffed clinics which can care for a large number of patients. All these perplexing questions and others as well must be decided in one way or another. They will tax the wisdom and ingenuity of our public health officers, of our hospital officials and of our medical authorities. The outcome of our campaign will in large measure depend upon just what decisions will be made.

My third and last debit item concerns research in syphilis and particularly experimental research. I am going to dis-

cuss this item in some detail for it is, I regret to say, not always sufficiently emphasized in discussions on syphilis control despite the contributions to our knowledge of the subject that can logically be expected from it.¹ Although it is a current opinion of the laity and of some physicians that all the important and fundamental facts regarding syphilis are known, this is far from being the case. It is true to say that we know a great deal about the disease. We know its causative agent and how it is spread; many features of its pathogenesis are well understood; its recognition is made relatively easy by the application of various diagnostic technics; and lastly, we possess acceptable methods of treatment. There is no doubt that the proper application of our present knowledge would lead to an adequate control of the disease. That this is so, however, should not make us forget the many gaps in our knowledge, the filling in of which might well revolutionize the entire future of the disease. The possibilities which might be realized are actually so significant that it is perhaps not too much to say that from a long range standpoint, the most important single step toward the eradication of syphilis is the prosecution of research. I shall not attempt to mention, let alone elaborate, all the various phases of the subject which might be investigated. The particular fields for future work which I have selected for the present discussion appear to me to be among those about which additional knowledge is urgently needed.

We need to know a great deal more about the etiologic agent of syphilis. The association of *Treponema pallidum* with the manifestations of syphilis is now well established and it is the opinion of practically all authorities that this organism is the causative agent. Certain observations, however, have suggested the possibility that the organism as we see it represents but one stage of a life cycle, the other stages of which are invisible or

¹ Chesney, Alan M.: Research Needs in the Control of Syphilis (Proc. Conf. on Ven. Dis. Control Work, Dec. 28-30, 1936). Ven. Dis. Inform., Suppl. 3, 1937, p. 63.

granular. If this theory should prove to be correct, it is evident that it will affect many of our present concepts of the disease. The question of carriers, for example, would have to be considered from a new standpoint.

We have been greatly handicapped in this and other lines of investigation in syphilis by the fact that up to the present all attempts to grow pathogenic or virulent *Treponemata pallida* in cultures have failed. The organisms which have been cultivated from syphilitic lesions have the appearance and motion of *Treponemata pallida*, but they are incapable of producing syphilis. The solution of the problem of artificial cultivation of pathogenic organisms would immediately open the way for a more complete understanding of the etiologic agent and the application of this knowledge could well have direct bearings on syphilis control. Is it beyond the bounds of possibility that a vaccine, protective or therapeutic or both, might eventually be elaborated?

From long clinical experience and from the study of experimental syphilis in animals during the past thirty years we have a considerable knowledge of the biology of the infection. There are many points, however, about which we are still quite ignorant. The entire question of the localization of organisms is practically unanswered. Why do the organisms localize in some organs and tissues and not in others? Why in one individual do organisms localize in a particular part of the body while in other individuals other parts are involved? Such questions are of particular significance with regard to involvement of the central nervous system and of the cardiovascular system. Some authorities have invoked the theory of "tropism"—that certain spirochetes possess selective affinities for certain tissues. Such a theory, however, does not offer any real explanation for the observed facts and no satisfactory proof has yet been advanced for the doctrine of specific strains of spirochetes. Furthermore, the implication of such a doctrine is that the biologic properties of a strain are fixed and this is to ignore a characteristic property of living matter, namely, variation.

There seems to be no doubt that constitutional differences are associated with differences in the manifestations of the disease. This has been particularly exemplified in clinical studies of white and Negro patients in this country. It is known, for example, that the incidence of cardiovascular syphilis in the Negro is relatively high while involvement of the central nervous system is a particularly prominent feature of the disease in white patients. It has long been thought that syphilis of oriental and tropical races is characterized by the comparative severity of secondary manifestations and by the comparative infrequency of central nervous system involvement. In experimental syphilis of the rabbit it has been shown that different breeds show differences in the clinical reaction to infection. The statement, however, that constitutional differences are reflected in the type of disease which develops does not explain the nature of these differences nor the manner of their operation. The subject is a fruitful one for investigation. There is the further question of the influence of environmental factors on the reaction to infection about which we know something but not a great deal. Additional studies along this line are likewise indicated.

An integral part of the entire subject of syphilitic disease concerns the nature of the defense reaction of the infected individual. We have abundant evidence from patients and from experimentally infected animals that individuals develop a greater or less degree of resistance to their infection. This protection, however, does not result, as far as we know, in the total elimination of spirochetes from the body even though it may be sufficient to cause the healing of lesions which have developed and to prevent the development of other lesions. Another aspect of the matter is the fact that in some individuals this acquired resistance is not enduring. For some unknown reason, it does not continue to be effective and relapses occur, that is, lesions develop. We know comparatively little of the mechanisms which are concerned in the defense reaction to syphilitic infection despite the efforts which

have been made to understand them. Since this aspect of the matter appears to be the master key to so many unsolved problems of the disease, it is to be hoped that continued research in this field will ultimately be crowned with success.

At the present time, syphilis control centers about the finding of persons who may spread the infection to others because of open lesions from which spirochetes are transferred by contact. The destruction of these spirochetes is the first aim of treatment. Further, our methods for adequate prophylaxis are built upon the principle of such transmission. It is by no means certain, however, that our present ideas regarding the transmission of syphilis tell the whole story. It is theoretically possible that infection may be contracted from sources that are less evident than a visible lesion. A more complete knowledge of the disease might show that virulent spirochetes can be discharged from an apparently intact mucous membrane. If such should be the case the question of the latent carrier and particularly the female latent carrier would take on a new and highly important significance. The effect on the epidemiologic aspects of the disease would be profound. While this is not the place to discuss the matter, I should like to mention that we do not know as much about syphilis in women as we should. That it differs in many important respects from the disease in men is well recognized but we understand very little of the reason for the differences.

The last point to which I shall refer is the treatment of syphilis. As I have already remarked, we now possess highly efficient, therapeutic procedures by which it is possible to treat satisfactorily the great majority of syphilitic patients. The drugs at our command have the requisite property of rendering the patient non-infectious to others, of causing the healing of lesions, and of preventing the development of other disease manifestations in a large proportion of patients. To accomplish these ends, however, it is necessary that treatment be admin-

istered over a long period—for months or years. This is definitely disadvantageous, an unfortunate feature of the present treatment of syphilis. And a further unfortunate feature is the expense involved. Certain of the drugs employed are costly and the total amounts which must be given are comparatively large. The cost is also increased by the fact that the patient does not give the drug to himself—he does not receive a prescription for a bottle of pills or a box of powders, which require no more equipment for administration than a glass of water and the patient's own power of swallowing. Each treatment must be given by a physician or a nurse. And it must not be forgotten that the satisfactory care of syphilitic patients is not limited to the antisymphilitic drugs administered, but that it includes other features, some of which involve expensive equipment. The long duration and the high cost of treatment weigh heavily against the easy accomplishment of our objective. I realize that the cost of treatment to the patient has been reduced to a bare minimum in many places and that it is actually free in others. But a considerable proportion of individuals are going to pay their own medical bills, and for the average patient the expenditure of the sums frequently charged for the care and treatment of syphilis simply cannot be made.

We must admit that the ideal treatment is still to be discovered. At the present moment, if I were asked what contribution to our forces for the control of syphilis is most urgently needed today, I should say a more effective method of treatment which would be both inexpensive and short. Of course, if such a method were a drug which could be given by mouth, it would be ideal, but this is perhaps too much to expect. In any event, it is generally agreed, I think, that research in the field of treatment for syphilis should be furthered by every means at our disposal.

From what has been said on the credit side of the outlook for syphilis control in this country, there is no doubt that a very

great deal is going to be accomplished in the immediate future. There will be a marked increase in the number of patients who will be efficiently treated and the incidence of syphilis will certainly be sharply diminished. It must be clearly understood, however, that these results will necessitate the sustained expenditure of enormous amounts of thought, of care, of time, and of money. The immensity and the complexity of the enterprise, however, were no reasons for not initiating the campaign and likewise are no reasons for not continuing it. And indeed, the present indications all point both to the continuation of the task and to the realization of its ends.

On the other hand, from what has been said on the debit side of the matter, I cannot be so sanguine about the results of a more remote future if by such results is meant that syphilis will be eradicated, or nearly eradicated, from our midst. Even under much more favorable conditions than now obtain, the accomplishment of such an optimum result is, in my opinion, rather dubious. In the event, however, that certain conditions were radically improved, as for example, by the discovery of a satisfactory method of immunization or by an ideal therapeutic procedure, the outlook for the distant future would become very bright indeed. To bring about highly desirable conditions for achieving the ultimate goal, I can see but one course to pursue, and that is the prosecution of continued research in all the unsolved problems of the disease. How this is to be accomplished is another story, but of its fundamental necessity there can be no doubt.

Our trial balance, then, is fortunately written in black, not red, figures. We are solvent. We can point with pride to our available capital of money, of service, of public interest and concern, and of knowledge—all of which appears to be sufficient to obtain results of a satisfactory order. But it is my contention that these results can be of the highest order only if a portion of our capital be expended upon less immediate ends, upon studies of problems that at first glance might appear to have little practical im-

portance. A more complete understanding of these problems is the contribution to the enterprise which research can make. When this knowledge is in our possession, the full control of syphilis may be more confidently predicted.

PUBLIC HEALTH ADMINISTRATION

Laws requiring premarital and pregnancy tests for syphilis. Reasons for and against. John A. Kolmer. J. A. M. A., Chicago. June 10, 1939, 112 2385.

A number of important questions are involved in recent legislation that has been enacted by a number of the States regarding premarital and pregnancy tests for syphilis. Kolmer considers the legal requirements for premarital blood tests are upheld by the following considerations: In view of the high incidence of the disease marriage inevitably involves syphilitic men and women. The rate of those who have been refused licenses because of syphilitic infection has already been reported in Illinois as 3.9 percent of the applicants. There will be a tendency to lower the incidence of syphilis. Some may be deterred from promiscuous sexual relations by the fear that their infection will become known when they desire to marry, but of greater benefit is the education of the public on the mechanism of genital and extragenital infection. The danger of transmission will be greatly reduced since more persons will come under treatment. Blood tests are the most valuable single means for the detection of the disease, especially after the primary or chancre stage. Many syphilitic persons give no history of infection and symptomless syphilis is comparatively frequent. The incidence of missed clinical diagnoses in the chronic stages with signs and symptoms of the disease is very high and properly conducted blood tests are invaluable aids

premarital blood tests will reduce the incidence of transmission of syphilis to spouse and children, and they will reduce the incidence of the economic hazards of marriage from incapacity or early death of the spouse. Although no study has been made of the relation of syphilitic infection in a spouse to divorce, Kolmer believes that it has much to do with many divorces. Premarital blood tests will greatly encourage the thorough treatment of syphilis, and they provide an excellent phase of the educational program against syphilis.

Kolmer discusses some of the arguments against such laws with which legislators are confronted. Blood tests may give nonspecific or falsely positive reactions, and unnecessary or injudicious treatment on the basis of positive serologic tests is an old story, especially in the case of physicians without special skill or experience with syphilis. Positive blood reactions as the only evidence of syphilis may not always indicate a danger to marriage, especially in the case of thoroughly treated chronic syphilis, and Kolmer advocates the recognition of this by simply refusing a license to all persons with positive serologic reactions when every reasonable precaution has been taken against false positive reactions. Marriage may be discouraged and sexual promiscuity be promoted by premarital blood tests. Blood tests alone may not detect syphilis, especially in its incubationary and primary stages, and Kolmer believes that the required time between the blood test and securing the license and actual marriage should not be longer than 10 days, and that there should be a physical examination of the applicants by a licensed physician.

Kolmer feels that there are no valid or important reasons against the legal requirement of blood tests during pregnancy or at delivery. One of the main purposes of such laws is to detect syphilis and institute treatment as early as possible for the welfare of the child. A test during pregnancy affords an excellent opportunity for detecting syphilis in both married and unmarried women. The detection and treatment of syphilis in preg-

nancy increases the chance of the birth of a nonsyphilitic child, with a reduction in the number of miscarriages and in infant mortality. The treatment of the mother provides indication for treatment during subsequent pregnancies. The detection of syphilis in the pregnant woman leads to a suspicion of syphilis in the child and to its treatment after birth. It may also lead to its detection and treatment in the father and other children.

Next steps in syphilis control. Thomas Parran. *Puerto Rico Health Bull.*, San Juan. May 1939, 3: 152.

Puerto Rico is an integral part of the United States and as such it shares in the responsibility and opportunities for better public health made possible under the provisions of the Federal Venereal Disease Control Act of 1938. The progress which Puerto Rico has been making under the leadership of Commissioner Garrido Morales, Doctor Quintero, and their associates in setting up the machinery to stamp out syphilis has been encouraging.

According to figures assembled by the territory's health department, 15 percent of the adult urban population of the Island are infected with syphilis. The Insular Department of Health is doing its part by setting up a central control office, with a venereal disease medical director, an epidemiologist, and other personnel. The ten field clinics, installed in those communities where the need seems to be most urgent, are offering facilities for diagnosis and treatment. The Puerto Rican legislature has appropriated funds to match the money made available through the appropriations of the Congress of the United States according to the provisions of the Venereal Disease Control Act.

Doctor Marion Sims, president of the American Medical Association 63 years ago, said that to control syphilis it must be regarded as a disease instead of a disgrace. It should be subject to the same regulations as other dangerous and contagious diseases.

To find and treat cases of syphilis adequately, the following public-health services are needed: (1) A trained public-health staff including a full-time medical officer to direct the control program, clinic physicians skilled in modern diagnosis and treatment of syphilis, public-health nurses to assist them, and field workers to find new cases and follow up lapsed ones; (2) reporting and follow-up of all cases of syphilis; (3) good treatment for patients with syphilis, even for those who cannot pay; (4) access to free laboratory service for physicians and clinics making blood tests; (5) distribution of free anti-syphilitic drugs to all physicians and clinics; (6) a required blood test for every expectant mother; (7) the requirement of medical certificates, including negative blood tests, before marriage; (8) the inclusion of blood tests in all complete physical examinations; (9) an adequate educational program aimed at age groups most frequently acquiring syphilis. Public education is the crux of syphilis control. People must learn to consult doctors or clinics, and shun drug-store remedies and self-treatment as worthless. The public must realize the cost of syphilis—in care, in wasted lives, in sorrow, and in dollars. The cheapest thing any community can do with syphilis is to cure it.

Results and implications of a county-wide syphilis survey. W. Frank Walker, T. Paul Haney, Jr., and H. C. Ricks. *Mississippi Doctor*, Booneville, June 1939, 17: 38.

A syphilis clinic was established in 1935 as a part of the general health program of Pike County, Mississippi, and in 1936 a cross-section survey was carried out through the cooperation of the County Medical Society and local physicians. As the incidence of malaria was high in this area coincident examinations for malaria were used for motivating people to submit blood specimens for examination. The project was explained to the different communities through public meetings, and there was a widespread interest taken in it.

Blood specimens were collected from 5,786 persons, which represented about 15 percent of the entire population. Of these, 413 (7.1 percent) were positive for syphilis, and of the positive specimens 146 were positive by one test only, 98 by two tests, 166 by all three tests and 3 were found positive but did not have all three tests run on them. An analysis by age groups, sex and color, shows that the peak of 1.8 percent is reached in the white males in the age group of 45 to 64, for the white females of 2.2 percent at 25 to 44, colored males of 20.5 percent at 45 to 64, and colored females 25.1 percent at 25 to 44. Interesting comparisons are made in figures from four other counties in surrounding states.

Applying the percentages of positives found in this sample to the entire population, there are probably 2,200 cases of syphilis in the county, of which approximately 250 are among the white persons, 1,950 among the colored, and these cases have 6,805 contacts who should be examined.

The health department has already begun to follow up the positives discovered in this survey; to date 150 cases have been followed and 455 familial contacts examined. For every positive case in the survey a little better than one additional case has been found in the immediate contacts.

Preparing for the premarital law. Mrs. R. V. Love. *Bull. Department of Health of Kentucky*, Louisville. April 1939. 11: 46.

The premarital health examination law enacted by the General Assembly of Kentucky in 1938 provides for an antenuptial physical examination to determine the presence of a venereal disease such examination to apply to both parties to a proposed marriage and to be made within fifteen days prior to making application for a license to marry. There may be many obstacles to the enforcement of such a law, but the women of Kentucky who fought for its enactment will do everything possible to see that such obstacles are overcome.

Although the law does not become effective until March 1940, much educational work is necessary if the measure is to prove successful. The public must be generally and accurately informed about the purpose of the law, how it operates, and what its proper enforcement will mean to the home and to the community.

Every woman's organization in the state should arrange for speakers who can intelligently explain the purpose and provisions of this bill to their respective memberships. These groups should sponsor public meetings to study and discuss the law and how everyone can assist in its enforcement. Public officials and health authorities will need all possible assistance in successfully carrying out its provisions.

Prostitution and venereal diseases.

Bascom Johnson. Health Progress, Freehold, N. J. May 1939, 6: 9.

Health departments are in the best position of any official agency to understand the relation of prostitution to the spread of syphilis and gonorrhea. If they were to follow the precedents furnished by their own successful attacks on other dangerous contagious diseases, they would initiate or support every practical measure calculated to dry up this reservoir of disease.

The subject of prostitution was exhaustively investigated by 26 States and municipal commissions before the World War. All of these commissions agreed that the policy of repression of commercialized prostitution was the only practical one. Three important principles of control of prostitution are: (1) Education—since the demand for prostitution creates the supply, young men must be educated in the necessity and practicability of self control, not only for their own sakes but for the community in which they live. Children's ideals and aspirations should be developed toward sane and wholesome sex living. This education must begin in the homes and extend into the churches and schools. (2) Law enforcement—the police and courts should concentrate their efforts on the enforcement of those laws aimed at

the third parties in prostitution: The racketeers, promoters, and the exploiters. These parasites are responsible for stimulating the demand for prostitutes to artificial proportions. When these third parties have been eliminated, prostitution is reduced to its simplest terms—the relation of the prostitute to her customer. Prostitution then becomes manageable. No prostitute should be allowed to make a public nuisance of herself or create a public scandal. If she avoids doing these things, she might well be left, as far as the police are concerned, to her own devices. (3) The protection of the public health—health departments will always have an interest in the prostitute as a potential spreader of disease. Diseased prostitutes should be treated by health departments in precisely the same way as their diseased customers—no better and no worse. All persons infected with venereal diseases, including prostitutes, should be required to take treatment and to refrain from exposing others to their infections.

This outline is in substance the program of the Scandinavian countries and they have achieved the lowest syphilis rate in the world. In these countries prostitution is not licensed, not regulated, and not tolerated, but it is steadily and consistently repressed.

Why report venereal disease? Edmund G. Zimmerer. Nebraska M. J., Norfolk. June 1939, 24: 204.

Among the reasons given by physicians for neglecting to report cases of venereal diseases are the following: (1) "It takes time and I am too busy," (2) "I forget, but I do report some of them," (3) "I haven't any supplies," (4) "I didn't know it was required," (5) "Lots of others don't report," (6) "I resent any outside interference with my practice," and (7) "I am not paid for reporting."

The most eminent practitioners of medicine and some of the busiest keep accurate case histories, are meticulous in reporting infectious diseases and answering correspondence, and yet have time to write numerous articles and books. Perhaps that is one reason for their

eminence. None of the quacks report. None of the abortion mills report their births. Many on the borderline of unethical practice hide from public notice by not complying with regulations. Some competent but careless physicians don't report venereal diseases. With which group does a physician want to be associated—the unethical or careless and incompetent physicians who do not report, or the cooperative and highest type of physicians who do report?

In Nebraska, the case of a patient with a venereal disease is required to be reported only by number. It is only the uncooperative patient who disregards his own welfare and the safety of his fellows who must be reported by name. Reporting cases of venereal diseases does not result in outside interference. There is no contact made by employees of the health department with the patient, no check made on diagnosis, no dictation or even suggestion as to the course of treatment except on direct request of the physician.

The physician in being granted a license or privilege to practice his profession has certain legal requirements and duties, among which is the statutory provision that communicable disease (including venereal disease) be reported. Society demands this as a right for its protection and not as a service for specific remuneration. Supplies for reporting are furnished without cost and no postage is required for the report card. The form is so brief that it requires less than 2 minutes for its execution.

Not a single objection to reporting can be sustained as worthy of consideration. There are, however, many good reasons for strict compliance with the regulation. One of the greatest obstacles to the evaluation of treatment procedures in the past has been the lack of accurate knowledge about the prevalence of venereal disease. Only complete reporting will ever enable the medical profession to achieve the goal of eradication of the diseases or even to plan the methods of attack according to need. Nebraska is doubtless being deprived of Federal funds allocated accord-

ing to need because of incomplete reporting in the past.

Reporting, especially of delinquent sources, and contacts, enables the department of health with the cooperation of physicians to secure more adequate treatment of patients and to procure the examination of suspects and contacts. This means less infection, fewer cases, fewer and milder complications and the ultimate eradication of venereal disease. Reporting is not an oppressive obligation. It is a public duty and a legal responsibility, but it brings the reward of a consciousness of having contributed toward the conquest of one of humanity's greatest scourges.

The teaching of syphilis. Joseph Earl Moore. J. A. Am. M. Coll., Chicago May 1939, 14: 137.

Prior to 1910 in practically all large hospitals in this country, teaching hospitals as well as others, the management and teaching of syphilis were undertaken in every outpatient and inpatient department. The patient with primary syphilis appeared in the different departments according to his symptoms and his sex, the diagnosis was arrived at on clinical grounds, and treatment was administered until the lesions healed. This was followed by a long period of latency and the patient appeared again in one of the medical clinics with complaints which might or might not be recognized as related to his previous syphilitic infection. Not only the diagnosis but also the treatment of syphilis was, therefore, widely dispersed. Discoveries concerning syphilis about 1903 to 1910 showed the desirability of centralizing the management of syphilis in a single department and this was carried out in most of the large hospitals.

As syphilis was managed prior to 1903 so it is still often taught. The student encounters syphilis in every department of the medical school, and in the clinical field in all the major departments of medicine and surgery he is faced with the differential diagnosis of the lesions of late syphilis. By this dispersion of in-

struction the student obtains widely varying and wholly inadequate ideas as to treatment. As it was formerly necessary to concentrate professional care of syphilis into a single department of the hospital, so it is now necessary to centralize its teaching. Until this is done information concerning the epidemiologic and public health aspects is not provided. At Johns Hopkins University School of Medicine the accomplishment of these aims is carried out comparatively simply. During his four years of training the student receives 60 hours of special instruction in syphilis, of which 12 are required and are didactic and semi-didactic; 48 are elective and practical.

The question of who shall teach syphilis is one which has caused much debate. Even prior to 1903, in France and Germany, syphilology had become closely associated with dermatology, but modern developments necessitate more than knowledge of dermatology. The necessary knowledge for a teacher of syphilology is a large order. A list of the medical schools in which syphilology has been separated from dermatology includes some of the largest schools in the country. Moore says it seems obvious, clear, and even elementary that the physician most capable of teaching syphilis is not necessarily primarily trained as a dermatologist, internist, or neurologist; instead, he should be one who knows something about syphilis in all its phases, whatever his original special training. He believes that the search for teachers of syphilis to medical students, then, should start not from a specialty of medicine, but from a man. What is wanted, he says, is not necessarily an "ist" of any sort but a physician whose major interest lies in an understanding of syphilis, its diagnosis, treatment and public health control.

Youth fights syphilis in a city health district. Report of a youth hygiene campaign in the Kips Bay-Yorkville District of New York City. June-December 1938. Margaret Cummings.

J. Soc. Hyg., New York. Apr. 1939, 25: 174.

Not a slum area, not Wall Street, not a factory center, but the home of 200,000 people, the Kips Bay-Yorkville district of New York City extends from 34th Street to 96th Street between Fifth Avenue and the East River. The Youth Social Hygiene Committee representing 30 local health groups of this district was established in June 1938 and for 6 months carried on a youth campaign against syphilis. Three sub-committees—research, publicity and finance—went to work and on October 21 a youth rally on syphilis was held at Julia Richman High School. Thirty other meetings were held which reached a total of 2,000 young people, most of whom were under 18 years of age. A clinic was open every Tuesday evening and over 100 tests were made there. Physicians were chosen as speakers at the meetings, and there was a large amount of exhibit material displayed for each gathering. General posters were widely distributed throughout the area.

How many meetings were held and who attended and how many posters were distributed is not so important as the fact that a group of 12 to 14 boys and girls, most of them between 19 and 22 years of age, gave their leisure time for 6 months to a project for improving the health of the community. The job was well done, and thousands of people in Kips-Yorkville learned about syphilis through the efforts of this committee.

Practical epidemiology of gonococcic infections in children. Theodore Rosenthal and Jacob Weinstein. *New York State J. Med., Albany.* Apr. 1, 1939, 39: 718.

It has been pointed out by Nelson that the epidemiology of gonorrhea should be much simpler than that of syphilis. The short incubation period of the former limits the number of persons who might be sources of infection.

Definite procedures in case finding have been established by Health Commissioner Rice in New York City. Each newly diagnosed case of gonorrhea reported to the

Bureau of Social Hygiene is carefully investigated and special efforts are directed toward the discovery of gonococcic infections in children. Cases of gonorrhea are generally investigated by public health nurses acting as nurse-epidemiologists.

Each original patient is personally interviewed to ascertain the identity of the person from whom he contracted the disease and of the persons to whom he may have transmitted the disease. Home visits are made to induce the suspected source and contacts to have examination and treatment. By persuasive methods it is usually possible to secure information and cooperation. Cases involving sex offenses against children are referred to the police authorities.

Gonorrhea in children seems to be most prevalent under the unsanitary conditions of overcrowded tenements, and little girls are more frequently infected than boys. Energetic efforts at case finding are successful in bringing to light new and unrecognized cases of gonorrhea. Any program for control of gonorrhea must employ direct methods of epidemiologic investigations to insure effectiveness.

Official proceedings, House of Delegates.

J. Kansas M. Soc. Topeka. May 1939, 40: 200.

During the spring of 1938 a course of lectures on venereal diseases was offered in each of the 12 Councilor Districts, sponsored by the Kansas State Medical Society, the Kansas State Board of Health, and the U. S. Public Health Service. In the fall of 1938 a brochure containing the material presented during the post-graduate course was published by the Kansas State Board of Health and a copy mailed to every physician in Kansas.

Four additional venereal disease clinics have been opened in Kansas—at Emporia, Salina, Leavenworth, and Parsons. The general conduct of the clinics and its policies are left entirely in the hands of the local medical society.

There has been an increase in the number of venereal disease cases reported to the Kansas State Board of Health. However, there is room for vast improvement

in the matter of reporting venereal diseases, especially syphilis.

During the spring of 1939 a second post-graduate course on syphilis and gonorrhea has been offered for physicians. It is hoped that a course of this kind can be offered annually.

The importance of a Wassermann test for syphilis made on every prospective mother during early pregnancy and the great advantage of having such a test on all persons contemplating marriage is the question above mentioned. The definite increase in the number of volunteer Wassermann tests from these individuals in Kansas, recently, reflects much credit on physicians of the State. It is to be hoped that this practice will become so universal that there will be no need for special legislation in Kansas.

Legislative results in Colorado. Rocky Mountain M. J., Denver. May 1939, 332.

Under the joint sponsorship of the Colorado Junior Chamber of Commerce, the Colorado State Medical Society, and other organizations, two antisiphilic measures, commonly known as the premarital and prenatal bills were enacted over negligible opposition.

House Bill No. 466 provides for examinations and serologic tests of applicants for a marriage license. Each applicant must file a certificate from a licensed physician stating that the applicant has been given an examination (including a standard serologic test for syphilis) made more than 30 days prior to the date of issuance of such license, and that in the opinion of the physician this person is either not infected with syphilis and other venereal diseases, or is not in a stage of that disease which may become communicable. This act is to take effect and be in force 6 months after the date of its passage—April 10, 1939.

House Bill No. 470 requires serologic blood tests for pregnant women. Every physician licensed to practice medicine who attends a pregnant woman in the State for conditions relating to her pregnancy is required to have a serologic test for syphilis made on a specimen of

oman's blood. Every other person permitted by law to attend pregnant women must have samples of blood taken for such serologic tests. In reporting every birth and stillbirth, physicians and others required to make such reports shall state on the certificate whether a blood test for syphilis has been made on a specimen from the mother and the approximate date when the specimen was taken. In no event shall the birth certificate state the result of the test. The General Assembly considered an emergency to exist, and the Act was made effective and in force from and after the date of its passage on April 10, 1939.

Protection of marriage and childlife against syphilis. William F. Snow. *Am. J. Syph., Gonorr., & Ven. Dis.* St. Louis. May 1939. 23: 277.

Thirty-three State legislatures are considering a variety of bills proposing new laws or revising existing statutes requiring health examinations, including syphilis tests, of both the man and woman seeking a license to marry. Eighteen States are considering bills requiring physicians to include a blood test for syphilis as part of their examinations in each pregnancy case under their care.

Not all of these legislative proposals are sound, timely, or adapted to practical administration; and many of them are not accompanied by appropriations or plans for providing competent personnel to carry them out effectively. Most of them are being promoted by the best elements of community leadership representing the home, the church, educational groups, and civic welfare groups.

It has been demonstrated that proponents and opponents of such legislation are usually divided on the basis of viewing the proposed legislation from (1) the assumption that the law itself is perfect and everything essential to carrying it out will be perfectly done, or (2) the assumption that the law is defective, incomplete, and cannot command trained public health and laboratory personnel or cooperation of either physicians or the public. Neither of these views is justified.

It is highly desirable that the passage of such laws be preceded by popular education and planning for continuing support. Those who argue for or against legislation should read the proposed law and apply their remarks to its actual provisions and administrative procedures which can be developed to give them full effect. This is frequently not the case; for example, the most widely reported and highly controversial debates on both premarital and prenatal laws have been based on the assumption that all such legislation would require merely one laboratory test of a blood specimen; and on the findings of this one test would depend the decision of the presence or absence of syphilis, and the withholding or granting of a license to marry. None of the students and recognized leaders of medicine and public health have approved such proposals. Only 3 or 4 States in past years have passed such a law, and these are up for amendment this year.

The author presents a synthesis of provisions of premarital and prenatal laws which have survived the test of practical administration in such manner as to warrant further trial and improvement. Such laws as those presented should be carefully prepared with regard to the constitutions and existing laws of each State; but it is believed that the provisions indicated meet fairly the objections voiced by persons who have studied the problems involved. Those who are opposed to all forms of compulsory health legislation will not be satisfied with any type of law which requires compliance with its provisions either by citizens or by those charged with the duty of carrying it out.

Conference on syphilis. Puerto Rico Health Bull., San Juan. May 1939, 3: 183.

The Department of Health of Puerto Rico organized a conference on syphilis which was held at Santurce on March 23, 1939. The purpose of the conference was to get together all the health officers, physicians in active practice, and laboratory workers to discuss the control, diag-

nosis, and treatment of syphilis in Puerto Rico.

Papers were presented by outstanding specialists. A round table discussion of the clinical aspects of syphilis and the correct interpretations and evaluation of the findings of laboratory tests was held. A demonstration was made of the management of one of the venereal disease dispensaries of the department of health, and cases in various stages of syphilis were presented. In the Central Biological Laboratory demonstrations were held showing the proper collection of samples of exudates for darkfield tests. The actual technics of the darkfield examination, the complement fixation test, and the Kahn and Kline tests were demonstrated. The 162 persons who attended the conference included 43 (26.5 percent) practicing physicians, 63 (38.9 percent) health officers, 7 (4.3 percent) medical laboratory directors, 11 (6.8 percent) physicians of the venereal disease dispensaries, 10 (6.2 percent) social workers, 19 (11.7 percent) laboratory workers, and 9 (5.6 percent) people interested generally in the problem of syphilis. A program of the conference is given.

Opening address at the conference on syphilis. E. Garrido Morales. *Puerto Rico Health Bull.*, San Juan. May 1939, 3:155.

For many years the Puerto Rico Health Department has recognized the importance of syphilis as a health menace, but principally because of the limited funds available it has been impossible to carry out successfully an effective program of control. During 1923 the Insular Legislature appropriated \$12,000 for this purpose, and two clinics were opened—one in San Juan and one in Ponce. Because of financial difficulties this amount was later reduced to \$6,000, making it necessary to close the clinic in Ponce and to reduce the amount of work carried on in San Juan.

Puerto Rico was not included in the provisions of the original La Follette-Bulwinkle Bill of 1938. A memorandum on the problem of syphilis in Puerto Rico

was immediately submitted to Congressional Representatives of the Division of Territories of the Interior Department and others took an active part in the hearing on this bill and as a result the benefits of the act were extended to Puerto Rico through an amendment introduced by Senator La Follette.

Pursuant to the provisions of the Act the Surgeon General of the Public Health Service allotted to Puerto Rico the sum of \$34,000 to be used during the fiscal year 1938-39. An additional appropriation of \$25,000 was obtained from the Insular Legislature. The following program was formulated: (1) Establishment of a Division of Venereal Disease Control under a trained full-time medical officer; (2) operation of 12 venereal-disease clinics distributed throughout the Island to provide diagnostic facilities and treatment for indigent persons; (3) intensification of the venereal disease work in the Public Health Units of the Department of Health, especially among patients attending pre-natal clinics, and provision for diagnostic and treatment facilities in 30 rural dispensaries operated by the Department; (4) blood examinations and treatment of cases of syphilis among more than 2,000 inmates of the insular penitentiary and 7 district jails; (5) educational campaign by means of newspaper articles, radio talks, distribution of literature, and the holding of institutes on syphilis control.

For the year 1939-40, it has been recommended that the Insular Legislature increase the appropriation for the control of venereal disease from \$25,000 to \$50,000. The Federal allotment to Puerto Rico will probably be increased, and the additional funds will provide facilities for a substantial expansion of the present program.

Compulsory versus voluntary methods of venereal disease control in Scandinavia, Holland, and Great Britain. Arthur W. Towne. *Am. J. Syphilis, Gonorr., & Ven. Dis.*, St. Louis. May 1939, 23: 348.

The author discusses a study of the methods of control of syphilis and gonorrhea.

area in Scandinavian countries and Holland made by a British Commission and published by the British Ministry of Health in June 1938. The purpose of this study was to secure information which might guide authorities in Great Britain in their venereal disease control work. The report leaves open the very important question as to which system of control, the voluntary or the compulsory, is inherently the more efficient. The Commission states that each country should employ such methods as are most acceptable and workable under its own national conditions, traditions, and psychology. It is conceded that compulsory laws and practices, according to the general judgment of Scandinavian officials and doctors, have proved effective in their countries. However, the Commission believes that compulsory regulations and methods would not fit into the requirements of Great Britain. The venereal disease control program of one nation cannot be arbitrarily transplanted to another country; the development must come from within and must be in conformity with national and communal needs.

British opinion concerning the merits of compulsory methods is sharply divided. A strong minority opinion is in favor of setting out compulsory notification and other coercive provisions.

An ideal system for the control and prevention of syphilis and gonorrhea should provide easily available, adequate, expert diagnostic and treatment facilities which should be so located and managed that patients are assured of a maximum of privacy and respect for their personalities. This means specially trained technicians and adequate financial support. In order to promote the discovery of new cases and prompt and necessary treatment, the public should be properly informed concerning the diseases through frank public discussion and modern educational propaganda.

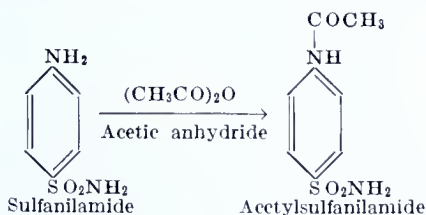
Both voluntary and compulsory methods are needed. Each patient should be dealt with on as nearly an individual basis as possible through a friendly, educative, suasive approach. Clinics and

private practitioners should be given the services of public health nurses, medical social workers, or other qualified field workers. Modern epidemiologic methods of finding sources of infection and new cases should be utilized. Public health authorities should maintain complete and intelligently analyzed statistical information concerning these diseases, both en masse and in respect to the relative effectiveness of different modes of control. For this reason and for other purposes as well, the official reporting of all cases of syphilis and gonorrhea should be made mandatory. There should also be legal authority for the proper use of compulsory measures (particularly for uncooperative patients) needed for providing treatment and preventing new infections.

LABORATORY RESEARCH

Acetylsulfanilamide. Its absorption, excretion, and toxicity in man. Nelse F. Ockerblad and Hjalmar E. Carlson. *J. Urol.*, Baltimore, May 1939, 41: 801.

With a daily dosage of 80 grains (5.2 gm.) of sulfanilamide as much as 90 per cent may be converted and excreted in the urine in the acetyl form (Helmholz and Osterberg). Acetylsulfanilamide (para-acetyl aminobenzenesulfonamide) may be prepared by the reaction of acetic anhydride on sulfanilamide.



Marshall, Cutting and Emerson found in mice that acetylsulfanilamide was more toxic than sulfanilamide. In large doses, acetylsulfanilamide produces dyspnea and an appearance of malaise in dogs with a

drop in the carbon dioxide combining power. In man acetylsulfanilamide can be given continuously in doses of 20 grains 4 times a day for at least 2 weeks with, at the worst, only slight toxic reactions. In man it produces a drop in the carbon dioxide combining power of the blood but produces no other blood chemical changes. Tables are included indicating that the rate of absorption and excretion of acetylsulfanilamide is slow. The maximum blood concentration obtained in man was 6.2 mg. percent. The maximum blood concentration of free sulfanilamide was 1.0 mg. percent 4 days following the administration of 20 grains of acetylsulfanilamide 4 times a day for 1 week.

No toxic reactions were noted in men with pathologic conditions. There was only a minimal degree of therapeutic effectiveness against acute gonococcal urethritis and in chronic prostatitis no demonstrable effect was observed. The striking difference in therapeutic effectiveness of acetylsulfanilamide compared with that of sulfanilamide shows what slight alteration in the molecule is necessary to produce a change in the activity of the drug.

Absorption, acetylation, and excretion of 2 sulfanilamido pyridine (Dagenan, M & B 693). Herbert E. Stockinger. *Proc. Soc. Exper. Biol. & Med., Utica*. Jan. 1939, 40: 61.

The name of this drug has been changed officially to sulfapyridine.

Analytical data are presented showing the fate of sulfapyridine in both laboratory animals and human patients. The original Fuller method was employed using sulfanilamide standards with a factor to account for the difference in molecular weight and color intensity of the pyridine derivative. Determinations of the conjugated form, 2(N-acetylsulfanilamido) pyridine, were similarly made after hydrolysis with p-toluenesulfonic acid.

It was found (as with sulfanilamide) that rabbits and humans detoxify sulfapyridine by acetylation; the dog excretes it completely and unchanged in the urine. In all three species the drug is detectable

in the blood stream directly after ingestion, and the unchanged, therapeutically active form is completely eliminated from circulation within 24 hours after the last administration, although the drug itself has but limited solubility in water (0.1 percent at 20° C.).

The conjugated form, 2(N-acetylsulfanilamido) pyridine, has been isolated from both rabbit and human urine. The crystals occasionally deposit spontaneously in such urine. A female patient, aged 67 years, was given 9.5 gm. of sulfapyridine over a period of 3 days, and 1.82 and 2.4 gm. of the crystalline acetyl derivative were recovered from two of her 24-hour urine specimens. Upon one spontaneous crystallization from alcohol the melting point of this compound was 226–227°.

Dosages were varied between the following rough limits: Human patients, 0.030–0.1 gm. per kg. per diem; rabbits, 0.16–0.64 gm. per kg.; dogs, 0.20–0.25 gm. per kg. No toxic effects of the drug were observed in the laboratory animals, but among human patients nausea was common and often accompanied by mental confusion which passed off upon withdrawal of the drug.

Blood analyses were made on 75 human patients between the ages of 5 and 70 years who had been given a dosage of 2.0–6.0 gm. of sulfapyridine per diem over periods varying from 3 to 22 days. In all cases in which no gastrointestinal obstruction was present, rapid absorption into the blood stream was observed and a balance among rates of absorption, acetylation and excretion generally was maintained after 24 hours. To insure maximum blood levels, samples for analysis were usually taken at least 24 hours after the initial dose. The amount of acetylated (inactivated) drug varied widely in different individuals (30 to 80 percent) but averaged about 50 percent. This was somewhat greater than that for sulfanilamide. Usually no free sulfapyridine was detected 24 hours after the last dose was administered and essentially all the acetylated form was eliminated within 24 hours. Urine analyses confirmed the findings.

concentration of sulfanilamide in spinal fluid and blood following single intrathecal injection of drug. E. Neter, D. H. Weintraub, and A. L. Dayman. *Proc. Soc. Exper. Biol. & Med., Utica.* Feb. 1939, 40:164.

Sulfanilamide is readily absorbed after oral administration and is found in the blood and spinal fluid. Usually the concentration in the spinal fluid is somewhat lower than in the blood.

This is a report of a study made to determine what concentrations of sulfanilamide are reached and maintained in the spinal fluid and in blood following intrathecal injection of the drug. Patients on whom a lumbar puncture was indicated for diagnostic reasons and whose spinal fluid was normal were given intrathecally 10 cc. of an 0.8 percent solution of sulfanilamide in physiologic saline solution. Four and 18 hours following this injection, lumbar punctures again were performed and blood specimens were also taken. The concentration of sulfanilamide in both spinal fluid and blood was determined according to the method described by Marshall, Emerson and Cutting.

The results obtained in 5 patients were essentially the same. From these observations it may be concluded that (1) it is possible to obtain a relatively high concentration (10-16 mg. percent) of the drug in the spinal fluid 4 hours after a single intrathecal injection of 80 mg. of sulfanilamide; (2) the drug is readily eliminated from the spinal fluid of these patients within 18 to 24 hours; (3) the concentration of sulfanilamide in the blood at the periods of observation is relatively low (1 mg. percent or less).

A new coupling component for sulfanilamide determination. A. Calvin Bratton and E. K. Marshall, Jr. *J. Biol. Chem., Baltimore.* May 1939, 128: 537.

The method proposed by Marshall, Emerson and Cutting in 1937 for the determination of sulfanilamide has been widely used in estimating the drug in blood and urine both in experimental work and in controlling the dosage of the

drug for patients. During the 2 years since the method has been in use, certain disadvantages have become apparent. The use of N, N-dimethyl-1-naphthylamine (dimethyl- α -naphthylamine) as the coupling component for the diazotized sulfanilamide is not entirely satisfactory because of the necessity of a catalyst for rapid development of color in dilute solutions, the need of a large excess of the reagent, and the necessity of a certain amount of alcohol to keep the resultant azo dye in solution. A coupling component which can be obtained in the form of a crystalline salt of reproducible composition and which gives a soluble azo dye in acid solution has appeared desirable. Another defect discovered in the method was that certain samples of dimethyl- α -naphthylamine did not result in complete recovery of sulfanilamide added to normal blood. This was found to be due to the salts (mainly chloride) present in the blood filtrate catalyzing the destruction of the azo dye by the excess nitrate.

The ideal coupling agent for determination of sulfanilamide should exhibit rapidly of coupling, sensitivity, purity, and reproducibility, be unaffected in rapidity of coupling by changes of pH from 1 to 2, and the azo dye formed should be acid-soluble and not affected in color by pH changes from 1 to 2. Preliminary tests were made with 17 compounds to determine for each (1) the rapidity of coupling (speed) for diazotized 0.1 and 0.01 mg. percent solutions of sulfanilamide buffered to pH 1.3; (2) the sensitivity with a 0.01 mg. percent solution; (3) the solubility of the azo dye with a 10 mg. percent solution; and (4) the effect of pH on the color of the dye in the same solutions used for determining the effect of pH on speed. Trichloroacetic acid was used for acidification, excess nitrite was destroyed with ammonium sulfamate, and pH was varied by adding excess acid or sodium dihydrogen phosphate.

Of the 17 compounds tested, N-(1-naphthyl)ethylenediamine dihydrochloride was found to be most suitable. It was readily prepared in a state of high purity,

and its coupling was rapid and uninfluenced by pH in the range of 1 to 2. This range of pH had no effect on the color of the dye, and the dye was more soluble in this range than any other coupler examined.

Thus, in the determination of sulfanilamide by diazotization and coupling in acid solution, the use of N-(1-naphthyl) ethylenediamine dihydrochloride offers the following advantages over N, N-dimethyl-1-naphthylamine (dimethyl- α -naphthylamine): (1) Reproducibility and purity, (2) greater rapidity of coupling, (3) increased sensitivity, (4) elimination of buffer, and (5) increased acid solubility of the azo dye formed. The authors present an improved synthesis and a complete characterization of the new coupling component. A slight modification of previous technic and application to other primary aryl amines are described.

Toxicity of M & B 693. Paul Gross & Frank B. Cooper. Brit. M. J., London. May 20, 1939, 1: 1058.

In this letter to the editor the authors state that they found urinary calculi composed of 6.4 percent sulfapyridine and 64.1 percent acetylsulfapyridine in a number of rats which received 0.5 to 1 gm. per kilogram of M & B 693 each day orally for 8 to 14 days. The resulting sequelae were in many instances partial to complete urinary obstruction with associated pyelonephritis and hematuria, and sometimes death. Antopol and Robinson have reported that similar calculi were caused by administering M & B 693 to rats, rabbits, and monkeys, but were not produced in mice or dogs.

The failure of Wien, quoted by Whitby (Lancet, 1938, 1: 1210) to observe urinary calculi in rats which received as much as 3 gm. per kilo daily for 15 days is difficult to explain. Although the formation of urinary calculi following the administration of M & B 693 is not exactly a "toxic" reaction, it deserves the serious attention of clinicians, since hematuria following treatment with M & B 693 has already been reported by Adalja (Brit. M. J., 1939, 1: 643).

Protective antibodies in the serum of syphilitic rabbits. Thomas B. Turner. J. Exper. Med., Baltimore. June 1939, 69: 867.

The presence of a relative immunity to man following infection with *Treponema pallidum* has been demonstrated by reinoculation, but most of the available information on immunity in syphilis has been gained from a study of the disease in animals. Turner reports on a series of experiments on rabbits which he summarizes as follows:

When an emulsion containing virulent *Treponema pallidum* is added to serum from normal rabbits and from untreated immune syphilitic rabbits that have been infected with a homologous strain of *T. pallidum*, the mixture incubated at 37° C. and injected intracutaneously into normal rabbits, typical syphilitic lesions commonly develop at the sites of inoculation of the normal serum-spirochete mixture while at the sites of inoculation of immune serum-spirochete mixtures usually either no lesion develops or else the incubation period of the resulting lesions is shorter and the lesions remain smaller than those produced by normal serum-spirochete mixtures.

In a series of preliminary experiments of 56 areas inoculated with serum-spirochete mixtures, in 42 the suppressive action of the syphilitic serum was manifested in 10 areas questionable evidence of protection was noted, and in 4 areas there was no evidence of a suppressive or protective action.

The protective action of the syphilitic serum seems to have been lessened by heating to 56° C.

The results of the protection test in other series of experiments were as follows: (a) Of 12 areas in 6 rabbits inoculated with normal serum-spirochete mixtures typical syphilitic lesions developed while in the same number of areas inoculated with immune serum-spirochete mixtures there was complete or partial suppression in all. (b) Of 45 areas inoculated with serum from 10 different immune syphilitic rabbits, definite evidence of protection was observed in 2

questionable evidence in 5, and no evidence of protection in 3. (c) Of 8 areas in 4 rabbits inoculated with immune serum-spirochete mixtures no lesions developed during the period of observation, while of 8 areas in the same rabbits inoculated with one or two normal serum-spirochete mixtures typical syphilitic lesions developed in each.

From these experiments Turner concludes that during the course of syphilitic infection rabbits develop specific humoral antibodies which can be demonstrated by an appropriate "protection test." The presence of these antibodies is associated with a high degree of acquired immunity to the disease.

Experimental study of arsenic resistance in syphilis. Francisco Lisi. *Gior. ital. di dermat. e sif.*, Milano. Apr. 1939, 80: 347.

The author discusses experiments on rabbits in which he attempted to determine the effect on syphilitic infections of giving small doses of arsenic over considerable periods of time before the infection. The arsenic medication was also studied after the infection to determine whether there had been a habituation that limited its effectiveness.

Male rabbits weighing 2000 to 3000 gm. were given 2 mg. of arsenic medication per kilogram of weight. After varying periods of time they were inoculated with syphilis and in some of the cases the treatment with small doses was continued after inoculation.

The administration of small doses of arsenic before inoculation seemed to a certain extent to inhibit the taking of the syphilis. It seemed also to a certain degree to lessen the effectiveness of the arsenic treatment given after inoculation.

The results of the experiments seem to indicate that the changes in arsenic resistance caused by administration of small doses of the drug are due to changes brought about in the host's body rather than to changes in the spirochetes induced by the drug.

Do syphilitic animals develop an immunity after treatment with neoarsphenamine? P. Gastinel, R. Pulvenis, and P. Collart. *Bull. Soc. franç. de dermat. et syph.*, Paris. March 1939, 46: 332.

As a result of their experiments with rabbits, the authors observed that intensive treatment with neoarsphenamine which is started as late as 90 days after infection will cause the disappearance of treponemes as demonstrated by negative gland transfers. Rabbits so treated can be reinfected with syphilis, the interval between the end of treatment and the time of reinoculation being the determining factor. Before 10 months reinoculations are positive in 3.3 percent (syphilomas). "Occult" infections occur in 6.6 percent. From the tenth to the twenty-fourth month (as long as observations were made) reinoculation is followed by the development of typical syphilomas in 33.3 percent of cases.

Relation of the constituents of Ducrey's streptobacillus to immunity and allergy. Mario Ronzani. *Gior. ital. di dermat. e sif.*, Milano. Feb. 1939, 80: 123.

The author discusses the question of the complex structure of the bodies of bacteria, taking up particularly the relation to immunity and allergy of the nucleoproteids and polysaccharids.

He studies in particular the constituents of Ducrey's streptobacillus. He describes the technic used for extracting the polysaccharids and nucleoproteids from pure cultures of Ducrey's bacillus. He found that on using Boivin and Mesrobian's trichloroacetic method a thermostable, acid-soluble substance presenting the characteristics of a glucid could be extracted from the bodies. This substance had a specific antigenic action in vitro and an allergenic action both in normal persons and in those with soft chancre. Using the method of Lustig and Galeotti a substance with the physico-chemical characteristics of the nucleoproteids could be extracted from the Ducrey bacilli which also had an aller-

genic action in normal individuals and in those with venereal ulcer.

From the results of his research the author concludes that both the glucid and nucleoproteid extracts of Ducey's bacillus have antigenic and allergenic properties. The allergenic and endotoxic properties of the bacilli are not attributable solely to either of these groups of constituents.

PATHOLOGY

Fatal agranulocytosis after sulphanilamide treatment. Brit. M. J., London. May 20, 1939, 1: 1031.

An obese woman of 60, receiving treatment for recurrent frontal sinusitis with prontosil album (p-aminophenylsulfonamide—3 half-gram tablets daily) died after receiving 34.5 grams within a period of 23 days. There was a period of 10 days following the discontinuance of the drug before death occurred. The day before the patient died a blood count revealed the following: Red cells—3,580,000 per cubic millimeter; hemoglobin—56 percent; white cells—600 per cubic millimeter (polymorphs 2 percent, lymphocytes 94 percent, monocytes 4 percent). The post-mortem examination of a film from the sternal bone marrow revealed many mononuclear cells, but no polymorphonuclear leukocytes. Immature and developing erythrocytes were found.

The fatal agranulocytosis in this case was probably caused by the occasional depressant action of the sulfanilamide group of drugs on the leukopoietic system. In this case the total dosage of 34.5 gm. in 23 days is low compared with the average total dose of 58 gm. in 7 fatal cases reported by Johnston (1938). The suggestion that the duration of the treatment is of greater importance than the total dosage is supported by the figures in this case. The cumulative nature of the agranulocytic action of the drug is emphasized by the latent period of 6 days that elapsed between discontinuing the drug and the appearance

warning symptoms.

On lymphogranuloma inguinale.

Bettinger (now Sidney). Virchow Archiv., Berlin. Mar. 17, 1939, 346.

The author made histologic studies (Canton, China) of the involved lymph nodes of 10 cases of typical lymphogranuloma inguinale. Macroscopically the inguinal lymph nodes were as a rule markedly enlarged and the individual glands fused together. Within most of the lymph nodes small abscesses containing yellowish-green mucopurulent material were found. These abscesses were more of a round than starshaped. Microscopically these abscesses are as a rule not true abscesses but consist of necrotic foci surrounded by epithelioid cells. Only a few leukocytes are found in the necrotic areas. Langhans giant cells were occasionally seen in the periphery. These lesions were larger than tubercles and never gave the appearance of fused tubercles. These foci of epithelioid cells were found not only in chronic, but also in early cases. The author states that in the sections of lymph nodes which he studied he was not able to find the inclusion bodies which have been described by Miyagawa and others. He does not agree with Hellerström and others who have observed marked similarity in the histologic findings of lymphogranuloma inguinale and tuberculosis. In syphilitic gumma the peripheral zone contains more connective tissue, and cells other than epithelioid cells are more numerous. The findings in chancroid and septic conditions do not resemble those of lymphogranuloma inguinale. In meningococcal smears and occasionally in the pus from buboes Miyagawa inclusion bodies were found. The author is not certain that they represent the virus of the disease and thinks that they may be a reaction product of some sort. Experimentally clinically characteristic buboes were produced in animals, but histologically the buboes showed atypical infiltrates in connective tissue. Histologic examination of the primary lesions of two

nts showed an atypical ulceration in e and a lesion resembling granuloma hereum in the other.

Experimental study of the histology of the Frei reaction. Filippo Franchi. *Riv. ital. di dermat. e sif.*, Milano. Apr. 1939, 80: 369.

As there is still a good deal of difference of opinion in regard to the significance of the Frei reaction, the author made attempts to determine whether its specificity could be demonstrated by histologic examination of the nodules produced by the antigen.

He took patients with intensely positive Frei reactions and inoculated them not only with Frei antigen but with streptococcus, staphylococcus, and gonococcus antigens. A table is given showing the results of the tests.

He found decided differences in the histologic picture of the lesions produced by the Frei antigen and those produced by the other antigens. Those produced by the Frei antigen had a distinctly tubercloid structure while those produced by the other antigens showed only the picture of an ordinary inflammation. The latter were only Brocq skin reactions showing that the skin of the patient with syphilis is particularly sensitive to various stimuli but the tubercloid nodules produced by the Frei antigen are specific.

Paraplegia from erosion of vertebral column by large thoracic aneurysm. Maximilian J. Hubeny and Percy J. Delano. *Radiology*, Syracuse. Feb. 1939, 32: 171.

Cases are few in which erosion of vertebrae by thoracic or abdominal aneurysm of the aorta has proceeded far enough to cause spinal cord symptoms by compression. The aneurysm usually ruptures before such extensive bony destruction takes place. The diagnosis of thoracic aneurysm is apt to be elusive unless there is a complaint of pain in the back, in which case roentgenograms make the case plain.

The patient in the case here reported was a Negro woman, 47 years old, who

gave a definite history of syphilis. Her blood Wassermann reaction had been positive but at the time of admission it was negative, and the spinal fluid proved to be positive. In 1936 she began to complain of pain in both legs, followed by weakness. She had become bedfast before her admission to Cook County Hospital in October 1938. Examination revealed a blood pressure of 262/170, with considerable left-sided increase in the heart's diameter; pathologic findings showed complete paraplegia from the level of D6 with complete sensory loss. She complained of dyspnea. A diagnosis of spinal cord tumor was made, and the routine roentgenograms showed a large out-pouching of the descending thoracic aorta, with erosion of the bodies of thoracic vertebrae four to eight. Two days later the patient expired after a sudden drop in blood pressure from 262 to 140 systolic and greatly increased dyspnea.

The autopsy findings showed that the anterior portion of the bodies of the fourth to eighth thoracic vertebrae were missing, having been eroded by a large, adherent aneurysm and sac, and the spinal cord was exposed in the region of the sixth and seventh vertebrae. An interesting factor in this case was that despite the extensive destruction of vertebrae, the patient had never felt pain in the back.

Syphilitic opticochiasmatic arachnoiditis.

Derrick Vail. *Am. J. Ophth.*, St. Louis. May 1939, 22: 505.

Basilar meningitis due to syphilis has been recognized for many years. Oppenheim, in 1911, stated that the chief form of brain syphilis is basal gummatous meningitis which usually arises from the subarachnoid tissue in the region of the chiasma. Later (1918) Igersheimer termed the region of the optic chiasm the favorite seat of basal syphilis. Just as the nonsyphilitic cases of chiasmal arachnoiditis have shown improvement or recovery by surgical intervention, so arachnoiditis due to syphilis has yielded to surgery with, in a few cases, improvement of vision. Thirteen (10 percent) of a series of surgically verified cases reported

by Bollack, David, and Puech had positive blood and/or spinal fluid Wassermann tests, and the post-operative results in 4 cases indicated improvement.

The author reviews 7 additional cases, 6 of which are presumptive. Three of the cases were diagnosed by neurologists as of tabes or taboparesis. A history of vascular lesions was obtained in 2 cases. The fields of vision showed defects that are considered to be characteristic of chiasmal involvement. The mixed type of optic atrophy seen in all the cases is one of the pathognomonic signs of chiasmatic arachnoiditis, and indicates a combination of simple atrophy and neuritis. The author feels that these cases indicate that if neurosurgery is performed before it is too late, improvement in vision may result. Hans Reese is quoted as saying that the more acute syndromes of this entity should be treated medically prior to surgical intervention, whereas a damaged optic chiasm with progressive field defects (low-grade reactivity in blood and spinal fluid) should be treated at first surgically and thereafter medically.

Preventive ophthalmology between the ages of twenty and forty-five. John H. Dunnington and Maynard C. Wheeler. *Preventive Med.*, New York. May 1939, 19: 31.

It has been estimated that syphilis causes 10 to 15 percent of blindness in adults, and 2 percent of all eye disease. Interstitial keratitis occurs in about 50 percent of patients with congenital syphilis, and about 25 percent of these cases have permanently poor vision (below 20/60). Syphilis causes 20 percent of all inflammations of the uveal tract including 30 to 40 percent of cases of iritis. Cases of iritis constitute 73.3 percent of the total number with eye complications due to early syphilis. Ocular manifestations occur in 2.3 percent of patients with early syphilis. Optic atrophy occurs in approximately 10 percent of patients with tabes dorsalis. The optic nerve is involved in 4.3 percent of patients with paresis. Syphilis is responsible for 12 per-

cent of the cases of papilledema. Ocular muscle paralyses are found in 12 percent of patients with neurosyphilis.

Interstitial keratitis due to congenital syphilis might be prevented by examining all pregnant women for syphilis and treating all those found to have the disease. After the keratitis has developed in a person with congenital syphilis, antisyphilitic treatment should be given in addition to local medication to prevent further complications of the disease.

Gonorrheal conjunctivitis in the adult is a much more serious affair than in the newborn. It is estimated that it occurs about once in every 700 or 800 cases of gonorrhea. About 17 percent of these cases result in blindness of one or both eyes. Every patient with gonorrheal urethritis should be warned about the dangers of such an ocular infection. When ocular exposure to gonorrhea is suspected, 25 percent argyrol should be instilled into the eyes. The disease is usually extremely severe and the cornea is often rapidly involved, so prompt treatment is imperative. It is much too serious a condition for the general practitioner to treat. The chief cause of destruction of vision in the disease is corneal ulceration. Early treatment, including prompt hospitalization, is the most effective method of preventing blindness. Sulfanilamide has been reported as an effective therapeutic agent for the condition. The disease is extremely contagious and known cases must be handled with every precaution by trained attendants.

DIAGNOSIS

Syphilitic reagin in blood and in spinal fluid. A comparative quantitative study. Alexander S. Wiener and Irving M. Derby. *Arch. Dermat. & Syph.* Chicago. June 1939, 39: 999.

The concentrations of syphilitic reagin in serum and spinal fluid were compared by a quantitative flocculation technic

series of 1,245 pairs of specimens which came from patients at the Brooklyn State Hospital for nervous and mental diseases suspected of having syphilis of the central nervous system. It was found that by the method used titers as high as 1:16 were attained in the blood serum, whereas the titer of the spinal fluid never exceeded 1:6. Moreover, the amount of reagin in any spinal fluid was practically always less than that of the corresponding serum.

These findings are of interest in connection with the site of origin of the reagin in the spinal fluid. In a previous paper the authors have presented the theory that the syphilitic reagin in the spinal fluid of patients with neurosyphilis is at least in large part formed locally, and the evidence presented in the present study favors this theory. It may be that the capacity to form syphilitic reagin (and other antibodies) is less highly developed in the central nervous system than elsewhere, possibly because of its small number of reticuloendothelial cells.

The results of the investigation should be of value to the clinician from the standpoint of diagnosing syphilis of the central nervous system. Thus, in the present series not a single case was encountered in which the initial diagnostic examination in which the Kline exclusion test on serum was negative and the flocculation or Wassermann test on the corresponding spinal fluid positive; and only 3 cases were found in which after treatment the Kline exclusion test on the serum was negative but the spinal fluid gave a positive reaction. Therefore, when the question of the presence or absence of syphilitic meningoencephalitis arises, this diagnosis can be practically excluded by examination of the serum alone when a positive test like the Kline exclusion test gives a negative result.

The role of the spirochaete in the Wassermann reaction. A. Beck. J. Hyg., London. May 1939, 39: 298.

The progress made in recent years in the technic of spirochete cultivation has

led to new investigations on the role of this organism in the Wassermann reaction. During the last two years routine examinations have been made in the author's laboratory with spirochetal antigens of serums sent in for the Wassermann test. Experiments have been carried out, to elucidate the following questions: (1) The specificity of the complement-fixation reaction with different types of spirochetes, (2) the antigenic value and serologic relationship in the Wassermann reaction of different culture strains of *Spirillum pallidum*, (3) the relation between the complement-fixation and agglutination reactions with spirochetes, (4) investigations of the nature of the spirochetal antigen.

The author summarizes the results of his study as follows: The examination of 1100 serums by both the Wassermann reaction and the complement-fixation test with spirochetes revealed a superior sensitivity of the latter reaction and practically equal specificity of the two tests. Syphilitic serum contains two different antibodies; one reacting with the lipoid antigen of the Wassermann reaction, the other with a specific antigen in the spirochete. The spirochetal antibody of syphilitic serum has a complex serologic structure, corresponding to spirochete strains of different antigenic make-up. The existence of this antibody and its specific absorption by the homologous antigen can also be demonstrated by agglutination. The difference between agglutinin titers found in normal and syphilitic serums is not pronounced enough to render this method satisfactory for the practical diagnosis of syphilis. The spirochete contains, apart from its specific antigen, the ubiquitous lipoid substance representing the Wassermann antigen. A fraction was obtained from spirochetes by Raistrick and Topley's method which in complement-fixation and precipitation tests reacted actively with spirochete anti-serums from rabbits, but which so far has failed to react with syphilitic serums.

Results obtained with the pallida reaction (Gaehdgens). Its diagnostic and therapeutic significance. L. Schleif. *Ztschr. f. Immunitätsf. u. exper. Therap.*, Jena. June 8, 1939, 95: 431.

On a total of 5,529 serums obtained from 3,078 patients, in all except 35 of whom there was a definite history of infection and antisyphilitic treatment, the pallida reaction (PR) was carried out simultaneously with the citochol (CR), the Meinicke clarification reaction II (MCR) and the Kaup modification of the Wassermann reaction (WR). Of 1,112 blood serums obtained from cases with a definite diagnosis of syphilis the WR was positive with 682 serums (61.3 percent), the flocculation reactions with 795 serums (71.5 percent) and the PR with 876 serums (78.8 percent). There were 161 of these serums (14.4 percent) which were negative with all the tests used. The PR was positive in 73.8 percent of cases of primary syphilis as compared with the WR which was positive in only 46.6 percent of such cases. In secondary syphilis it was 11.9 and in latent syphilis 21.3 percent more sensitive than the WR. In comparing the flocculation reactions with the PR, the citochol reaction was found to be even less sensitive than the WR but the MCR was only 8 percent less sensitive than the PR. In congenital syphilis it was even superior to the PR in sensitivity. In quantitative tests the PR and WR were found to be approximately parallel. The greater number of positive reactions with the flocculation tests as compared with the WR was due to a large number of weakly positive reactions obtained with the former. The WR was falsely positive in 1.4 percent, the flocculation reactions in 1.84 percent, and the PR in 1.14 percent of the 4,276 serums obtained from nonsyphilitic persons. The non-specific reactions were particularly frequent among patients with gonorrheal arthritis, skin tuberculosis, skin carcinoma and drug exanthemata. There was found to be a relationship between non-specific reactions and markedly increased sedimentation rate of

red blood corpuscles. The PR failed to diagnose only 1 case of central nervous system syphilis as compared with WR which failed in 8 and the flocculation reactions which failed in 7 of 10 cases examined. The positive PR was more resistant to the influence of spirochete treatment than the other reactions.

The diagnosis of syphilis in the laboratory. O. Costa Mandry. *Puerto Rico Health Bull.*, San Juan. May 1939, 162.

The author discusses the various laboratory procedures used in the diagnosis of syphilis. An announcement is made that the biological laboratories of the Department of Health of Puerto Rico will cooperate with clinical pathologists and serologists on the Island in the standardization of their technics. Reagents will be supplied and specimens will be taken for check-up purposes. With the establishment of a venereal disease clinic near the Central Laboratory at San Juan with the cooperation given by the Director of the Division of Venereal Diseases it is possible to check the results of serologic tests with clinical work.

Precautions against hemolysis set for Florida Health Notes, Jacksonville, May-June 1939, 31: 55.

Hemolysis is the dissolution of the red corpuscles of the blood, freeing the hemoglobin and producing a reddish-colored serum. Marked hemolysis produces an opaque deep red serum preventing accurate serologic reading so that the specimen must be discarded. Hemolysis may be caused by physical, chemical or bacterial factors—extremes of heat or cold, excessive shaking, a drop of water, traces of acids or alkalis, alcohol, or bacterial growth. During digestion of food absorption blood serum is cloudy due to the presence of chyle. Blood specimens should be collected in the morning before breakfast or several hours after a meal when the serum is clear. The following suggestions will prove valuable in preventing hemolysis: (1) Allow the blood containing the blood to stand in a slant

ation at room temperature until the
clots (1 to 3 hours) and then store
in the refrigerator until it is ready for
ling; (2) forward specimens to the
laboratory by the quickest route; (3) re-
ve the needle from the syringe before
pumping the contents into the test tube
to expel the contents as slowly as pos-
sible to prevent mechanical break-down
of the red corpuscles; (4) be sure that
the needle, syringe and test tube are per-
fectly clean and dry—if not dry then
sterilize them in a physiologic saline solu-
tion; (5) if the patient's red blood cells
clot more easily than normal the
serum may be poured off after the clot
forms and only the serum sent to the
laboratory.

Problems of gonococcal infection. Present status and future outlook. Russell D. Herrold. *Am. J. Syph., Gonorr., & Ven. Dis.*, St. Louis, May 1939, 23: 19.

The advent of successful chemotherapeutic measures has reduced the medical management of gonococcal infections to a few main issues: (1) Proper evaluation and standardization of accepted chemotherapeutic agents as well as newer ones that are being developed; (2) making more generally available the present diagnostic methods of smears and cultures, which will require closer cooperation between physicians and laboratories.

Biologic and immunologic research seems to offer comparatively little of value except in a more complete understanding of the mode of action of chemotherapeutic agents, particularly in the greatest deficiency of that group of persons who are relatively resistant to chemotherapeutic measures. This group will increase in size as more efficient chemotherapeutic agents are found.

The carrier problem is very important in the management of gonococcal infections, particularly in the female. It requires three methods of attack: (1) Improvement by technologists in the methods of examination of smears and cultures; (2) education of physicians concerning the importance of the problem,

and making more accessible competent laboratories where physicians may obtain these examinations; (3) education of the public concerning the fact that subclinical states of infection are frequent, so that satisfactory cooperation can be obtained more easily by physicians in private practice as well as by those in clinics.

The author suggests that sulfapyridine may replace sulfanilamide in the treatment of gonorrhea. Several reports have been published in England indicating that sulfapyridine is more effective than sulfanilamide in gonococcal infections.

In vitro, there appear to be 6 clear-cut factors in the explanation of the mode of action of sulfanilamide: (1) The concentration of the drug, (2) the species of bacteria, (3) the possible variation of strains, (4) the number of bacteria, (5) the duration of contact, and (6) the environment. The above factors may probably be transposed to a similar explanation of the action of sulfanilamide in vivo. The variable environment of the host probably has a direct influence on the bacteria. If there is an unfavorable environment in the host, the addition of sulfanilamide might produce a summation of the two antibacterial agents. The primary mechanism may be explainable on the basis of a deleterious effect on bacterial metabolism, thus interfering with the propagation of bacteria. Lysis might follow such lethal influences.

The problems relating to the diagnosis of gonococcal infections will be solved only by the development of more efficient and more accessible laboratory technologists. Physicians in general either lack such specialized training or they cannot afford the time or expense needed for thorough examinations. Further improvement in cultural methods is desirable. The future use of cultures routinely will prove highly effective not only in the medical phase of the epidemiologic control of gonococcus infections, but as a potent educational influence on public opinion regarding the seriousness of the problem of gonococcus carriers.

Gonococcus culturing in public health laboratory practice. Mabel M. Malcolm and C. E. Dolman. Canadian Pub. Health J., Toronto. May 1939, 30: 252.

The results are presented of an investigation (extending over 22 months) which was planned to determine both the practicability of gonococcus culturing in a very overcrowded public health laboratory and the comparative efficiency of the cultural and smear methods in detecting residual gonococcal infection. Specimens were received from patients with gonorrhea attending the Vancouver Clinic of the Division of Venereal Disease Control, Provincial Board of Health of British Columbia.

Over a trial period of 22 months, 5,391 cultures and corresponding smears were examined. Specimens came from both the cervix and urethra of 780 females and from the prostatic secretion of 1,558 males. A chocolate-agar medium, portable incubators, and the oxydase reaction were used. Cultural and smear examinations were both negative in 3,975 (73.7 percent) specimens. Positive cultures but negative smears were obtained in 751 (13.9 percent) and suspicious cultures but negative smears in 395 (7.3 percent) specimens. Positive or suspicious cultural findings were therefore associated with negative smears in 21.2 percent of all specimens examined. Approximately one percent of all specimens showed positive or suspicious microscopic findings although the cultures were negative.

In the whole series, there were 946 positive cultures, but only 236 positive smears; and there were 419 suspicious cultures but only 34 suspicious smears. There were thus 5 times as many positive and suspicious cases of residual gonococcal infection detected by the cultural method as by the method of direct microscopic examination. Cultural findings revealed 461 definitely-infected persons and an additional 187 possibly-infected persons who would have been discharged as presumably cured on the usual basis of absence of clinical or direct microscopic evidence of gonococcal infection.

In cases of suspected residual infection the cultural method proved of equal sensitivity on specimens from male and female patients. Out of a group of males, 394 (26.2 percent) had positive or suspicious cultural findings with negative smears. Of 780 females with positive or suspicious cultural findings, 209 (26.8 percent) had similar findings.

The fact that 80 percent of all positive cultures were associated with negative smears indicates the serious inadequacy of the hitherto-accepted criterion of cure in gonorrhea and emphasizes the urgent need for providing public health laboratories with facilities for gonococcus culturing before patients are considered cured.

The authors do not suggest that direct microscopic smear examination should be abandoned. In the laboratory diagnosis of early acute gonorrhea, smears are probably reliable enough to make unnecessary the far greater inconvenience, and labor of routine culturing. It is possible that some positive smears associated with negative cultures might be obtained in some cases of gonorrhea, because the gonococci may be all intra-cellular or made otherwise non-viable by abundant pus. A series of parallel smear and cultural examinations might profitably be carried out on this type of case.

TREATMENT

The treatment of gonorrheal ophthalmia neonatorum in general practice. Scheerer. Med. Klin., Berlin. 24, 1939, 35: 233.

The author outlines the following procedure for the diagnosis and treatment of gonorrheal ophthalmia neonatorum. Material for a smear is to be removed from the eye by means of a platinum wire which has been cooled off or with a sterilized glass rod. The cornea should never

hed. Care should be taken when the lids are opened that the pus, which is held between the lids under considerable pressure, does not spurt into the miner's eyes. It is advised that a methylene blue stain be made, and the exact method of preparing the solutions and carrying out the staining procedure are described. In establishing the diagnosis it is also important to get the history of the parents regarding the infection. In gonorrheal ophthalmia the discharge from the eye is first watery and amber colored, soon becoming creamy pus. Pseudomembranes may occur but are usually very delicate. The lids are often tremendously swollen and hold the pus under considerable pressure. The author does not advise irrigation of the eyes because in order to carry out this procedure the lids have to be held apart with a mechanical device (Desmarres's lid holder) which may injure the cornea. The stream of the irrigating solution may also damage the cornea. A careful examination of the cornea should be made when the patient is first seen in order to determine whether it has been damaged. If there has been no corneal damage, this should not occur as result of treatment. If only 1 eye is involved, the child should be placed in a position which does not permit the pus from the affected eye to flow across the nose into the unaffected eye. It is best to protect the healthy eye with a watch-glass bandage which has a small opening on the temporal side. The normal eye has to be kept under observation and smears taken from it from time to time. For the treatment of the affected eye two persons are needed during the first 24 to 36 hours. Every 10 minutes the exuding pus should be wiped from the lids by means of cotton dipped in 3 percent boric acid solution, so that the lids will not adhere to each other. The lids should be drawn slightly apart before but not during the wiping, so that as much pus as possible can escape. Small pieces of gauze saturated with ice water are then placed over the eye and changed every few minutes, both day and night. After 24 to 36 hours the edema

of the lids has decreased to such an extent that they can be spontaneously opened which means that the danger of corneal injury is over. Boric acid ointment is now applied to the lid margins to prevent their adhering. Besides the above mentioned treatment, 1 drop of 10 percent protargol solution is instilled into the eye morning and evening. Smears are made every few days. If in 3 different smears made on 3 consecutive days no gonococci are found, cure has been established. This usually occurs after 16 days. If cure is delayed one-fourth percent zinc sulfate solution should be instilled into the eye for several days, and following this the procedure should be repeated with protargol. Because of by-effects (paralyses) that may be produced by albucid, this drug should not be used in the infant. Breast feeding should be continued.

The minimal effective concentrations of arsenic and bismuth compounds on *T. pallidum* in vitro in relation to the therapeutic dose. Harry Eagle. *Am. J. Syph., Gonorr., & Ven. Dis.* St. Louis. May 1939, 23: 310.

It was previously shown that "arsenoxide" (m-amino-p-hydroxyphenylarsenoxide), bismuth compounds, arsphenamine, neoarsphenamine, and silver arsphenamine actively immobilize and kill pathogenic *Treponema pallidum* in vitro. The question arises as to whether the concentrations found to be effective in the test tube are comparable to those attained in the body after the therapeutic administration of these drugs, and thus, whether their curative effect in syphilis may be due to a spirocheticidal action similar to that observed in vitro.

In the course of preceding studies it was found that an increase in the concentration of the drug, in the time of exposure, or in the temperature at which the mixture of spirochete suspension and drug was incubated promoted the anti-spirochetal action, while an increase in the concentration of tissue extractives markedly inhibited the immobilization of the organisms.

The inhibitory effect of tissue extractives on the antispirochetal action of arsenic and bismuth compounds in vitro was determined in the presence of the edematous ooze from a rabbit chancre, which presumably corresponds in composition to the intercellular fluids at the inflammatory focus. Under these conditions "arsenoxide" had a definite antispirochetal action within 1 to 2 hours at a temperature of 25° to 34° C. in concentrations of approximately 1:1,000,000 to 1:4,000,000; arsphenamine, neoarsphenamine, and silver arsphenamine were similarly effective in concentrations of 1:250,000 to 1:1,250,000; and 2 water-soluble bismuth compounds were effective in concentrations (expressed as bismuth metal) of 1:50,000 to 1:225,000.

The antispirochetal action of these compounds increased approximately twofold with a 10° C. rise in temperature. The concentrations of the various compounds necessary to immobilize the organisms decreased markedly as the period of observation was prolonged. It follows from these considerations that the minimal effective concentrations just cited are several times greater than those which would have been necessary if the experiments had been carried out for 8 hours at 37° C.

The author discusses the satisfactory correlation between the experimentally determined minimal effective concentrations of these arsenic and bismuth compounds in vitro and those which may be attained in the tissue fluids after their therapeutic administration.

Mapharsen in the treatment of syphilis complicating pregnancy. A comparative study. Mario A. Castallo, John A. Coppolino, A. E. Rakoff, Paul H. Roeder, and Glenn S. Dickson. *Am. J. Syph., Gonorr., & Ven. Dis.*, St. Louis. May 1939, 23: 332.

A group of 116 pregnant women with syphilis were treated with mapharsen and bismuth during pregnancy. Twenty-six were primigravidas, none of whom had received previous treatment. Among the multigravidas, 22 had received treatment in earlier pregnancies.

Treatment consisted of weekly intravenous injections of mapharsen, usually of 40 mg., and intramuscular injections of bismuth salicylate in oil. A total of 849 injections containing 31,940 mg. mapharsen were given.

There were 106 (91.4 percent) births in the group. Of 76 patients who received 6 or more treatments, 72 (94.7 percent) had live births. There were 41 (83.7 percent) live births among patients who started treatment before the sixth lunar month. The live births among 43 patients who received optimal treatment (started injections before the sixth lunar month and received 6 or more injections) numbered 39, or 90.7 percent. This was no better than the results for the group at large.

There were 10 (8.6 percent) fetal deaths, 7 being stillbirths and 3 miscarriages. Six or more treatments had been given the mothers in 4 instances; 3 mothers had 5 injections each; the remaining 2 had 1 and 2 injections respectively.

There were 25 positive cord Wassermann reactions among 46 such tests made. In 5 of these cases fetal death had occurred. Ten of the remaining 19 were available for serologic follow-up; only 3 subsequently had positive blood Wassermann reactions.

Fifty of the 106 babies born alive followed up in the pediatric clinic. (47.1 percent) the Wassermann reaction became positive.

Nausea and vomiting followed the few injections in almost every patient. Persistent gastrointestinal reactions were frequent, occurring in 66, or 56.9 percent of the group. In 6 cases these were so severe that the drug was discontinued. Relative or actual loss in weight was common. In one patient a papular dermatitis developed and in another a toxic anemia developed, both of which disappeared after the withdrawal of mapharsen. There were no nitritoid reactions.

The results are compared with those obtained in similar groups of patients who had been treated with neoarsphenamine, acetylarsan, and quinine bismuthate. It is concluded that of the

gs, neoarsphenamine is the drug of choice for the treatment of syphilis complicating pregnancy.

In this study mapharsen has not been as effective as neoarsphenamine in the treatment of syphilis in pregnancy because it does not afford as good protection to the fetus during the period of treatment, an equal number of healthy infants does not result from the treatment, and mapharsen very frequently causes disturbing gastrointestinal symptoms with a relative or actual loss of weight. However, the treatment of syphilitic pregnant women with mapharsen will insure a high percentage of live births and will greatly reduce the number of infants who would have been infected with syphilis if no treatment had been given.

Iron in the treatment of gonorrhea of the female. W. Kirchner. *Zentralbl. Gynäk.*, Berlin. April 22, 1939, 63: 67.

Uliron or Diseptal A were the only drugs used in the treatment of 39 women with gonorrhea. In the group which did not respond to this type of treatment no other therapy was used. The dosage was that advocated by Schreus. There were 87 percent of cures among the 15 uncomplicated cases and 86.7 percent of cures among the 24 cases with complications.

Treatment of early syphilis. Harold N. Cole. *Bull. Genitoinfectious Dis.* Boston. May 1939, 3: 1.

In cases of early syphilis the earliest possible positive diagnosis should be made preferably by 1 or more daily dark-field illuminator examinations of the tissue juices taken from the suspected primary lesion. If these are negative it is then necessary to depend on a serologic diagnosis. These tests should be made weekly until such a period of time has elapsed that there is no longer danger of a submerged syphilis infection becoming active.

Treatment of the patient with early syphilis should consist of alternating

courses of injections of a suitable arsenical drug and a bismuth preparation, given continuously until 30 to 40 injections of each are administered. During the first week, 3 intravenous injections of an arsenical should be given—dosage 0.2 gm., 0.3 gm., and 0.4 gm. of arsphenamine; 0.3 gm., 0.45 gm., and 0.6 gm. of neoarsphenamine; or 0.03 gm., 0.04 gm., and 0.06 gm. mapharsen. This is followed weekly thereafter with intravenous injections of 0.4 gm. of arsphenamine, 0.6 gm. of neoarsphenamine, or appropriate doses of mapharsen until 10 injections have been administered. It is advisable to administer an injection of a bismuth preparation with the first few arsenical treatments and with the last such treatment in the course.

The bismuth salt to be employed for the routine weekly treatment should be a liposoluble compound or a suspension in oil (such as potassium bismuth tartrate or bismuth subsalicylate). The dosage should be such that from 80 mg. to 130 mg. metallic bismuth is administered each week. Ten weekly treatments constitutes a course.

Routine serologic tests should be made at the end of each course of treatment, and 2 or 3 days after the first injection of an arsenical in a course a Wassermann test (provocative) should be made. A cerebrospinal fluid test for syphilis should be made early in the course of the disease and repeated at the end of one year or more if the first test is negative. If, under the routine treatment, blood tests become negative, treatment should be continued until the tests have been negative for one year. If, at the end of this period, careful physical examinations, cerebrospinal fluid tests, and radiologic examination of the cardiovascular system do not reveal signs of syphilis, the patient may be placed on probation and followed up quarterly with serologic examinations for one year and thereafter twice a year. With such a routine an early case of syphilis will be clinically cured in a large percentage of cases.

The comparative effects on early syphilis of combined and of alternating treatment. Walter Beekh and Charles W. Barnett. *Arch. Int. Med.*, Chicago. May 1939, 63: 974.

In the last 10 years in the syphilis clinic of the Stanford University School of Medicine two plans of treatment have been used for early syphilis. Formerly, treatment was carried out with alternating courses of nearsphenamine and iodobismittel but recently a system of combined therapy resembling the simultaneous method described by Stokes has been used. The authors give the results of treatment in a series of 81 patients given the combined therapy compared with the results in a series of 256 patients receiving the alternating type. The effectiveness of the treatment was appraised on the basis of the serologic response, the incidence of involvement of the nervous system and the incidence of serologic or clinical relapse.

The frequency of serologic reversal at the end of 5 and of 18 months of treatment was slightly greater for the patients given combined treatment than for those given the alternating type. The authors feel that this is of minor importance, since the rate of serologic reversal is not a satisfactory index of therapeutic efficiency. The incidence of abnormal cerebrospinal fluids was the same in the two series. The incidence of relapse, both clinical and serologic, was greater for the patients given the combined treatment. When the factors of regularity of treatment, total dosage of drugs and duration of observation are taken into consideration, this difference becomes significant. Since the prevention of relapse is the most important indication of efficiency of treatment, the authors believe that the inferiority of the combined type of therapy in this respect is sufficient to make further use of this type of treatment undesirable.

The treatment of acute gonococcal salpingitis. J. Herman Long. *M. Clinics North America*, Philadelphia. Mar. 1939, 23: 345.

In this clinical discussion, Long places treatment under the classification of: (1)

Physical; (2) thermal; (3) foreign protein; (4) bacterial; (5) chemical.

(1) Complete rest in bed, in a hospital if possible, should be advised immediately after the diagnosis is made. Fowler's position is best and should be forced copiously.

(2) Probably the greatest benefit of douches is derived from the temperature of the water. The Elliott treatment applies prolonged dry heat to the vagina. It requires hospitalization of the patient or daily visits to the physician's office. Long and Long believes it to be no more effective for an abscess high in the pelvis than hot douches. The diathermy method of thermal treatment is a valuable therapy in many cases but it is probably most useful in combination with other forms of therapy. Cold applications have no value in the treatment of acute pelvic infections. Artificial fever, induced by mechanical means, is indisputably of doubtful value. Long believes its use in combination with other methods of treatment, using lower temperatures for short periods of time, will lessen dangers and add to effectiveness.

(3) The use of foreign protein injections stimulates the defense mechanism of the body and the inflammatory processes are more rapidly brought under control.

(4) The first enthusiastic reports of the use of Corbus-Ferry broth filtrate have been replaced by those that report it does real harm.

(5) While sulfanilamide therapy is short of the ideal method of treating acute gonococcal salpingitis, Long says it probably approaches it more closely than any other method at present, certainly more closely than any other method of chemotherapy. In the Johns Hopkins Hospital 120 patients with acute or chronic salpingitis have been treated with sulfanilamide, the majority responding favorably to the drug.

Conservation of vision. J. Indian A., Indianapolis. June 1939, 32: 3

The Committee on Conservation of Vision of the Indiana State Medical Association has outlined a program to re-

incidence of blindness in Indiana. The important preventable causes of blindness are ophthalmia neonatorum and syphilis.

The Indiana State Board of Health refuses that a prophylactic agent be used against ophthalmia neonatorum but makes no definite recommendations as to what drug to be used. Argyrol, mercuramine, silver nitrate, metaphen, merthiolate, or even breast milk may be employed. Some 30 States are advocating distributing one percent silver nitrate solution in collapsible beeswax ampules; this seems to be the most logical drug available at present. The Indiana Academy of Ophthalmology has passed a resolution recommending this agent.

The incidence of ophthalmia neonatorum is entirely too high. Fifteen percent of the children in the State School for the Blind, and 2½ percent of those on the blind pension rolls in Indiana are victims of the disease. In one Indiana town of 100,000 population, the hospital records revealed 10 of these cases within the last 5 years. Many milder cases are not hospitalized. In order to stamp out these diseases in children all cases should be reported to the health officer, and adequate ophthalmologic and nursing care should also be available for cases of gonorrheal ophthalmia in older persons.

There are 192 people in Indiana, or 8 percent of those on the total blind pension roll in the State, who are blind from syphilis. The syphilis control program does much to reduce this number, and Indiana physicians are urged to prevent, discover, and thoroughly treat patients with the disease. Prenatal blood tests would help to prevent interstitial keratitis and optic atrophy.

Discussion of sulphonamide therapy in gonorrhoea. A. J. King. *Brit. J. Ven. Dis.*, London. Apr. 1939, 15: 106.

In opening the discussion at the meeting of the Medical Society for the study of venereal diseases, Doctor King said his expressed views are based on preliminary impressions and will most certainly be subject to future modifications. He believes M & B 693 is much more potent,

therapeutically, than any of its rivals. At the Whitechapel Clinic nearly 300 male patients who had acute gonorrhoea have been treated with this drug, and in over 90 percent the infection was controlled and the signs and symptoms disappeared in less than 3 weeks. Reactions were rarely severe enough to necessitate termination of treatment. All but 50 of these patients were also treated with urethrovaginal irrigations. Study of the case reports shows that the results were not in any way inferior when irrigations were withheld. Albucid was administered to 41 male patients and the toxic effects were very slight. Only 2 of 11 patients who were given 4½ gm. daily for one week without urethral irrigations made a prompt and satisfactory clinical recovery, but 15 of the 17 who received the same dosage over the same period combined with urethral irrigations were clinically free from infection at the end of one week.

King does not believe that there is justification for withholding the commencement of treatment. He has found no reason to believe that patients who relapse after treatment with sulfonamides have sustained damage to or inhibition of the mechanism of immunity or have become "sulfonamide-resistant." Uleron has the disadvantage that it can be employed only in short courses so that relapse is very probable if the drug is used at the onset of the symptoms. The dangers of sulfonamide therapy are certainly far less than those resulting from the administration of arsenicals in the treatment of syphilis. Probably the sulfonamides do not directly kill the gonococcus but so modify the rate of reproduction of the organism that the body defenses are enabled to get the upper hand and the signs and symptoms of the infection disappear.

Discussion of sulfonamide therapy in gonorrhoea. A. J. Cockkinis. *Brit. J. Ven. Dis.*, London. Apr. 1939, 15: 117.

Cockkinis regrets the tendency among medical men to run one sulfonamide compound against others; judgment should not be pronounced until sufficient material has been accumulated—perhaps 1,000

cases might be regarded as adequate. He has seen a genuine relapse occur as long as 8 months after complete early cure without any evidence of disease in the intervening period.

After considerable study and analysis of cases he says that he would treat a patient with gonorrhea in the first week of infection with M & B 693; if in the second week, he might prefer sulfanilamide; in the third week he would consider uleron. He does not feel that provocative tests of cure are as important as some believe; a long period of observation of the patient is as important as the tests.

Cokkinis briefly summarizes 1,037 followed-up cases of gonorrhea in the male treated by him with sulfanilamide or M & B 693. Of the cases treated with sulfanilamide in the first week of infection there were good results after one course in 48 percent, and with M & B 693 in 77 percent. In the second-week cases sulfanilamide gave good results with one course in 77 per cent and M & B 693 in 85 percent. An analysis of the late relapses suggests caution and longer experience in the use of M & B 693; 9 percent of those treated with M & B 693 had late relapses as against 2.3 percent of the longer-observed sulfanilamide cases. The figures for the subacute cases indicated that inadequate or unsuccessful treatment with one sulfonamide compound leads to resistance to subsequent treatment with large doses of the same or of another compound.

Acetarzone therapy in one hundred and eighty-seven cases of congenital syphilis, with observations on a group of eighty-seven patients receiving no treatment. Donald M. Pillsbury and H. Harris Perlman. *Arch. Dermat. & Syph.*, Chicago. June 1939, 39: 969.

The status of acetarzone given by mouth as a preventer of late congenital syphilis has by no means been settled. The chief objections to its use are that the difference between the toxic and the therapeutic dose is too small, that the drug is still in an experimental phase,

that in many cases the physician can be certain that the drug is actually administered when given at home. In favor of its use are the argument that the drug is easily administered, the response on syphilitic lesions is good, serologic response is good, and reactions are usually serious.

For the series here reported the schedule of Bratusch-Marrain seemed to be the best available. For newborn infants the use of a system based on water is essential; unfavorable reactions are reduced but not entirely prevented by this means. The effect of acetarzone on infectious lesions seemed distinctly slower than that of arsphenamine. It was no more rapid than that of a soluble bismuth salt. The effect on interstitial keratitis was disappointing. There was no case of late clinical relapse but clinical progression of the disease despite of treatment occurred in 8 percent. The effect of acetarzone alone in reducing the Wassermann and the Kahn reaction of the blood was only moderately satisfactory for infants under 6 months of age (70 percent) but as good as that of standard preparations, or better in patients over this age (36 percent).

Nephritic reactions occurring suddenly and insidiously are the greatest drawback to acetarzone therapy. The authors do not believe that the treatment should be resumed after such a reaction. In general the occurrence of gastrointestinal and dermatitic reactions does not contraindicate further treatment. The incidence of all reactions was 10.5 percent of the patients treated. The incidence of reactions in hospital patients and outpatients was 31.8 percent for the former and 8 percent for the latter; this is probably due to the fact that the drug was not given as directed in their home. The evaluation of the responsibility of the parent or guardian is, therefore, one of the most important features of treatment by mouth, and lack of cooperation by the parent is a contraindication to acetarzone therapy. Regularity of attendance at the clinic was shown to be increased when oral therapy is substituted instead of injection.

the 187 cases of congenital syphilis in this series, 87 were under medical observation for an average of 3 years before antisyphilitic treatment was given, clinical relapse occurred in 22. Of patients admitted before the age of 1 the diagnosis was not made before the first birthday in 25. Since the authors find that the diagnosis of congenital syphilis will be missed in at least 6 of 10 unless a serologic test is performed, they consider a routine serologic test an absolutely essential part of an adequate diagnostic study.

From these data the authors conclude that the effect of acetarsone in arresting congenital syphilis is inferior to that of arsphenamine and bismuth preparations; the incidence of reactions is high, and the administration to outpatients is not assured.

In the discussion, Doctors Cole, Dennie and Kulchar all agree with the authors' conclusions. Before acetarsone therapy is discarded there should be further investigation, especially in the laboratory.



Venereal Disease Information

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The Quantitative Kahn Reaction

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Facts Regarding the Quantitative Kahn Reaction

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Ann Arbor, Mich.

1. The quantitative Kahn reaction gives the titer of syphilitic serum in the same way as the Widal (agglutination) reaction gives the titer of typhoid serum. Physicians want to know the agglutination titer of typhoid serum, whether the titer is 20, 80, 320, 640, etc. Similarly, many physicians want to know the titer of syphilitic serum, whether it is 2, 4, 10, 220, 360, etc. A positive (or four plus) report on a given serum merely means that the serum falls within an arbitrary positive range; the report does not tell how potent the serum is. Only by quantitatively determining the titer of the serum is its potency established.¹

2. The quantitative titer of a syphilitic serum is obtained by making a series of dilutions of the serum with salt solution and determining the highest dilution giving a positive precipitation reaction. The titer is so computed as to correspond to plus signs. A titer of 4, 40, or 400 may be said to correspond to 4 plus, 40 plus, or 400 plus. The titer of a serum depends on the concentration of syphilitic antibodies (or reagin) in the blood stream. The concentration of antibodies, in turn, is believed to depend on the degree of syphilitic activity in the patient, on his capacity to produce antibodies,

and upon other factors. Of two patients giving positive serologic reactions the serum titer of one might be as low as 2 and that of the other as high as 1,000. Obviously, a physician should know these facts in the diagnosis and treatment of his patients.

3. The quantitative reaction should be of value in the diagnosis of questionable cases when patients give no history nor clinical evidence of syphilis. There are insufficient records available as to the diagnostic value of positive serologic reactions accompanied by high titers, such as 40, 200, 360 or higher, compared with positive reactions accompanied by low titers, such as 2, 3, or 4. But it would seem reasonable to assume that high titers are of greater diagnostic value (in the absence of a history and clinical evidence) than low titers.

4. The quantitative reaction should prove of value also in the diagnosis if there is a history or clinical evidence of syphilis. All indications are that low, moderate, and high titers correspond, in most instances, to low, moderate, and marked syphilitic activity. An outstanding exception to this generalization is when the patient is literally overwhelmed by the spirochetes and an excessive amount of antigenic material is thrown into the circulation. When this situation occurs, antigen-antibody union may take place in vivo causing the antibody titer to drop.

5. The quantitative reaction should be employed in all conditions in which positive serologic reactions are obtained in the absence of syphilis. It would prove of great importance to establish the

¹ In a previous publication on the quantitative reaction (Kahn, Reuben L.: *The Kahn Test—A Practical Guide*. Baltimore, Williams and Wilkins Co., 1925, p. 132) the term "serologic units" was employed in expressing results. It is believed that "titer" is a more desirable term, since it is universally used in expressing the results of agglutination and other immunologic tests.

NOTE.—From the University Hospital, University of Michigan.

titers of positive reacting serums in leprosy, malaria, infectious mononucleosis, and other nonsyphilitic diseases. Indications are that the titers in these diseases are low, but no experimental evidence in this regard is available.

6. The quantitative reaction is especially helpful in antisymphilitic therapy. A patient's serum giving a positive reaction might show a titer of 320 before treatment and perhaps titers of 280, 160, 80, 20, 4 and finally a negative reaction after the patient has been given courses of therapy. Thus, does the physician have a quantitative serologic record of his patient at any time during the entire period of therapy.

7. The quantitative reaction may throw light on the efficacy of various methods of therapy. Under a given method of therapy, a patient might show a gradual reduction in the titer up to a given point. The patient before treatment might show a titer of 560 and, after several courses of treatment, a titer of 120. Then, instead of further reductions in the titer as treatment is continued, a gradual and persistent reversal in the titer is noted; the titer may rise to 200, 280 and, let us say, to 360. When this situation occurs it is evident that the particular method of treatment employed is not having a reducing effect on the titer, and a change in the method of therapy would suggest itself.

8. The quantitative reaction may indicate the oncoming of a relapse in a syphilitic patient under treatment. Instances have been observed in which a sudden rise in the titer during treatment proved to be the forerunner of a relapse. This rise in the titer may precede the relapse by some weeks.

9. The quantitative reaction is often helpful in serologically resistant cases. Records are available in which during two or more years of therapy of syphilitic patients, as many as 20 serologic reports were obtained, each marked "positive" or "four plus." These 20 reports might have led to the assumption that the patients were "serologically fast." But the quantitative results in

these cases revealed that at the initial serologic examinations, the patient titers were relatively high, ranging from 200 to 800, while at the twentieth examinations the titers were close to zero, ranging from 2 to 4.

10. The quantitative reaction frequently shows an immediate effect of therapy which is temporary and a late effect of therapy which is more permanent. The immediate (several days) effect of therapy is often provocative in nature and tends to raise the titer, while the later (several weeks) effect of the therapy is a reduction in the titer.

11. The quantitative reaction should help throw light on the interpretation of a therapeutic test. Thus, a patient may have a positive serologic reaction but no other evidence of syphilis. The quantitative test shows that the serum titer is, let us say, 4, 20, or 40. The patient is given a therapeutic test and quantitative determinations of the serum are made at frequent intervals, such as every other day. Since, in most instances, therapy causes changes in the titer of a syphilitic patient, it would seem reasonable to assume that a therapeutic test followed by such changes has greater diagnostic value than a therapeutic test which causes no change in the titer.

12. The quantitative reaction given to a patient is not always directly related to the severity of the clinical picture which presents. A patient with a tertiary lesion in the skin may show a relatively high serum titer, and a patient with cardiovascular syphilis may show a low titer. Comparatively slight syphilitic activity in the heart will call forth a correspondingly low serologic titer although the patient may be very ill. Comparatively marked syphilitic activity in the tertiary lesion in the skin will call for a correspondingly high serologic titer although the patient may show but little evidence of illness. It is thus evident that the severity of the clinical picture is dependent not so much upon the extent of syphilitic activity as upon the particular tissue attacked.

13. The quantitative reaction in relation to the standard Kahn reaction. Quantitative titers are reported to physicians only on those serums giving positive reactions with the standard Kahn test.

TABLE 1—*Relationship existing between standard and quantitative Kahn reactions*

Report of standard Kahn reaction to physicians	Laboratory reading of standard Kahn reaction	Report of quantitative Kahn reaction to physicians
		<i>Titer</i> 4, 20, 40, 80, etc.
Positive.....	++++ 1 +++++ ++++	13 2 1
Doubtful.....	++	1
Negative.....	± 0	0

¹ In rare instances a three plus reading shows a quantitative titer somewhat greater than 3.

14. The quantitative reaction on spinal fluids is likewise of value in the diagnosis and therapy of neurosyphilis. Different spinal fluids giving positive serologic reactions show wide variations in their respective titers, and these titers show a gradual reduction following therapy.

Summary.—The routine use of the quantitative Kahn reaction (in addition to the standard diagnostic test) gives promise of clarifying many obscure phases in the diagnosis and treatment of syphilis and neurosyphilis.

PUBLIC HEALTH ADMINISTRATION

American Youth Congress Supports Public Health Service Syphilis Control Program.

Representatives of 4,700,000 young people meeting at the Congress of Youth in New York City over the week-end of July 4, 1939 voted support of the Nine-

point Community Syphilis Control Program of the Public Health Service, went on record urging the full \$7,000,000 appropriation for 1941 as authorized under the LaFollette-Bulwinkle Act, and recommended the establishment of more extensive prenatal and postnatal clinics as well as suggesting that sex education and preparation for marriage be included in public school curricula.

Resolutions adopted by the 736 delegates were:

Whereas, the venereal diseases are one of the leading threats to youth health; and

Whereas, the effective control of syphilis requires community programs embracing all phases of prevention, diagnosis, and treatment facilities, legal measures, and education; therefore,

Be it resolved, That the individuals and organizations represented in this Congress of Youth actively work for adoption in every community of the Nine-point Community Syphilis Control Program of the United States Public Health Service.

Whereas, at the Model Congress of Youth in Milwaukee in 1937 the American Youth Congress recognized the peculiar importance to youth of the control of the venereal diseases; and

Whereas, Federal funds are needed to supplement State moneys for the development of adequate venereal disease control programs; therefore,

Be it resolved, That the individuals and organizations represented in this Congress of Youth support the appropriation of \$7,000,000 for control of the venereal diseases in 1941 as authorized in the LaFollette-Bulwinkle Act of 1938.

We recommend, The establishment by Public Health authorities of more extensive prenatal and postnatal clinics. Education in the proper care of children should be included.

We recommend, That instruction in sex education and preparation for marriage be included in the public school curricula. We also recommend that instruction be given in maternal health care.

Control of venereal and other communicable diseases. Evaluation of the industrial hygiene problem of the State of Colorado. Board of Health of the State of Colorado. Denver, 1939, p. 11.

Because the control of syphilis is a major public health problem, the Colorado State Board of Health has attempted to determine how much interest industry has taken in this problem. In making the industrial hygiene survey of Colorado, the State Board of Health asked plant owners or superintendents the following questions pertaining to syphilis control: (1) Were serologic (blood) tests made on all applicants for employment? (2) Were serologic tests made on employees annually, every 6 months, or at other times? ("Other times" usually means whenever the industry deemed it advisable for the employee to be given such an examination). (3) What disposition was made of recognized cases? (4) Were plants willing to cooperate with the Colorado State Board of Health in a venereal disease prevention program?

Of a total of 526 plants surveyed, 41 (7 percent) required serologic tests for syphilis of applicants for positions. Of the 36 plants (6.8 percent) which required serologic tests of employees, 7 plants required such tests annually, 19 plants required them every 6 months, and 8 plants required them at other times. Employees (with syphilis) of 7 plants were treated at the plant, such employees of 16 plants were referred to family physicians, infected employees of 7 plants were treated at clinics, and infected employees of 3 plants were discharged. In no instances were infected employees ignored. A total of 483 (93 percent of the 526) plants stated that they would cooperate with the Colorado State Board of Health in a venereal disease control program.

Even though an employee has a positive blood test it does not mean that he is a public health menace. Only the person who refuses treatment for early syphilis or whose treatment is irregular should be considered dangerous to the

community. If an employee with syphilis is taking proper treatment and is not physically handicapped by the complications of late syphilis, he is as good a risk to the employer as a person who is not infected. Unless this fact is recognized by the employer, not only will an venereal disease control program in industry fail, but a grave injustice will be done to the efficient worker.

Examination for evidence of gonorrhea

Health News, Albany. June 26, 1939, 16:102.

Many more cases of gonorrhea have been reported in males than in females whereas approximately the same number of males and females are reported to have syphilis. Since the transmission of both diseases usually occurs in the same way, it is reasonable to conclude that gonococcal infections in the female are being overlooked. Although gonococci are not found in many specimens in which pus cells indicate an inflammatory lesion, it is quite probable that the patient is infected by the gonococcus. In such cases additional specimens should be collected for microscopic examination the day following cessation of menstruation. Cultural examinations are recommended if there are approved local laboratory facilities.

The failure to find gonococci does not exclude gonorrhea. Therefore, patients with inflammatory lesions of the genital urinary tract should be considered potential sources of infection. In addition to the clinical observations and results of laboratory examinations a knowledge of the complete history and environmental conditions of a person is important for a proper evaluation. Patients with inflammatory lesions in which gonococcal infection cannot be definitely excluded should be considered infectious and should be kept under observation until it is reasonably certain that they are in a noncommunicable state. They should return for examination at stated intervals or at any time that there is evidence of recurrence.

Report of committee on venereal disease control. Proceedings of the 66th annual meeting of the Florida Medical Association, Inc. J. Florida M. A., Jacksonville. June 1939, 25:608.

The State Director of Public Health and his assistants have been very active in instituting control measures for the eradication of venereal diseases in Florida. This applies especially to publicity measures. Physicians have been supplied with postage-free, self-addressed envelopes for reporting venereal diseases. Printed forms giving complete instructions for the treatment of syphilis in most of its manifestations and stages are sent to private physicians. More clinics have been established for the treatment of indigent venereal disease patients and plans are under way for others. The drugs required in the treatment of syphilis are being furnished to county and city health officers for indigent patients. The health department, it is felt, could do more to discourage the treatment of venereal diseases by those who are not licensed to do so. Members of the committee have been particularly active in presenting programs for the education of the public and a great deal has been accomplished in this line. It is felt that the keynote of prophylaxis is the education of the public.

Serological laboratories. Public health. West Virginia M. J., Charleston. July 1939, 35:27.

The West Virginia State Health Department, on May 24, sent to all licensed physicians and medical societies a list of laboratories approved at that time for performance of tests for syphilis in connection with the recently enacted statute relative to premarital examinations. There has not been sufficient time since the enactment of the law to approve, or even inspect, all the laboratories which have applied for approval. In order to facilitate this approval, a series of 50 or more specimens taken from clinically and serologically known syphilitic cases and from known normal persons are being sent to laboratories throughout the

State for examination in parallel with two control laboratories. Following examination of the test specimens the laboratories obtaining the most accurate results will be inspected. The examination of the test specimen series has already revealed that some laboratories in the State are reporting a high percentage of positive serologic results on known normal persons and an unfortunately high percentage of negative results on known positive specimens.

2,000,000 blood tests. Illinois Health Messenger, Springfield. June 15, 1939, 11:96.

The number of blood tests for syphilis performed in the diagnostic laboratories of the State department of public health will pass the 2 million mark some time late this summer. The test was first offered in the summer of 1917; 48 specimens were submitted and tested by the Wassermann method in that year. From that small beginning the number of tests now averages about 25,000 per month.

During the first full year of the service, 1918, there were 1,419 blood tests for syphilis performed in the State diagnostic laboratories. Ten years later, 1927, the number had climbed to 42,550, while for the fiscal year ended June 30, 1938, the number was 268,563. The growth in the demand for blood tests is indicative of a growing confidence in the reliability of the procedure and in popular interest in the control of syphilis.

Voluntary public health nursing agencies in the State program for the control of syphilis. Public health nursing. Health Officer. (Multilithed.) U. S. Pub. Health Serv., Washington. June 1939, 4:90.

The experience gained during 1938 in a cooperative program between the Rhode Island State Department of Public Health and the voluntary generalized public health nursing agencies has demonstrated the soundness of the principle that the generalized public health nurse can and should have an important place in the program for the control of syphilis

and gonorrhea. The director of the bureau of preventable diseases found that these nurses were of great assistance in holding cases and in reducing the delinquency rate. The directors of the nursing agencies say that the syphilis follow-up program has definitely strengthened the family health program. The nurses are generally known to the family and the confidence of the family is swayed by her efforts to bring recalcitrant patients back to treatment. The nurses feel competent to include syphilis follow-up in their generalized programs, and the families visited, as a rule, appreciate the services of the nurse in this particular respect.

Key to syphilis control—patient cooperation. Helen Woods. Health Officer. (Multilithed) U. S. Pub. Health Serv., Washington. June 1939, 4: 68.

Syphilis cannot be conquered by simple means of regulations and routines but only by skillful employment of practical measures. The treatment of known infected persons, discovery of unknown infections in other persons, and the prevention of new infections are the accomplishments necessary. The patient, coming for medical care usually because he desires to be made well, loses something of his independence when he places himself under regular treatment. If he is made to feel like a social menace he stands in a fair way to become a social enemy. If self-respect is destroyed, fear and resentment are sure to follow. There must be compulsive measures to keep some patients in attendance for their treatments, but too ready and general enforcement measures can not only lose the diagnosed cases of syphilis but also discourage others from seeking medical care.

Case finding by means of an epidemiologic investigation of contacts is undoubtedly the most difficult part of any syphilis control program. The search depends entirely upon the patient's willingness to reveal information, and it is unnatural and a departure from cultural mores for people to discuss their sexual

activities. An authoritative approach to contact-tracing is entirely impracticable and thoughtless. Success depends upon rapport with the infected patient; control can be achieved through the patient because in the last analysis it is he who holds the reins. The most vital factor in the syphilis control program depends on our ability to enlist the interest of the patient beyond the immediate matter of his own illness and its treatment.

Discovery and control of syphilis is not practical through the family approach. Young persons today live independently of their families and have their intimate contacts outside of the home. There has usually been little danger of transmitting the disease to family members since accidental infections are rare.

The mistaken interpretation of "innocent infections" has led to the belief that syphilis can be easily acquired by very casual contact. This has undoubtedly been a factor in the unnecessary dismissal of many domestic servants. Educational efforts should be directed toward making information more clear and accurate, rather than giving more information. The patient himself should receive education, for every well-informed syphilitic patient who is satisfied with his treatment is a potential force in the dissemination of valuable knowledge and of syphilis control.

Summer courses and new curricula in public health. Pub. Health Review Ann Arbor. June 15, 1939, 8: 65.

Through the cooperation of the University of Michigan Medical School and Division of Hygiene and Public Health and of the Detroit Department of Health (Division of Venereal Diseases) a program of study in venereal disease control is to be offered at the University of Michigan during the academic year 1939-40.

This program of study is open only to graduates of approved schools of medicine. Laboratorians who desire further training in the laboratory aspects of venereal disease control will take the

work under a different curriculum (Public Health Laboratory Methods).

The degree of Master of Science in Public Health will be granted upon the satisfactory completion of this program of study plus 3 months of practical experience in a public health agency where a recognized program of venereal disease control is being carried on. The curriculum includes required courses on sex education, physiologic hygiene, communicable diseases and epidemiology, public health statistics, public health law and administration, sanitation, acute infectious syphilis, gonorrhea, administration of a venereal disease control program, serology of syphilis and gonorrhea, and chronic syphilis. Additional elective and substitute courses are open. A total of 30 semester hours of work is required.

Trainees holding appointments for one semester only are permitted to enroll in those courses which will prepare them for immediate services in the control of venereal diseases. However, all students are advised to qualify for the master's degree as soon as possible, and one year appointments of trainee students are recommended.

Sick insurance and venereal diseases.

Maerz. Sozialhyg. d. Geschlechtskr., Leipzig. May 1939, p. 18.

The author discusses the importance of a campaign against venereal diseases. On the basis of the last census in 1934 a yearly increase of 225,000 persons with venereal diseases (syphilis 50,000, gonorrhea 175,000) was found. If this number is added to that of those already infected, about 500,000 such persons are under medical treatment during the year. The total yearly cost of venereal diseases was estimated by Reiter in 1933 to be 250 million Reichsmarks. From 4,000 to 5,000 congenitally syphilitic children are born every year. A decrease of about 40,000 births per year can be attributed to the venereal diseases. On the basis of 44 years' observations, the Gothaer Life Insurance Company found that morbidity and mortality due to various diseases was much higher

among syphilitic than among nonsyphilitic persons. If the average mortality of all the insured (including syphilis) is set at 100, the following figures are obtained for those with syphilitic infections: 160 due to malignant new-growths, 164 to diseases of the kidneys, 184 to gastro-intestinal diseases, 216 to cardiovascular diseases, 222 to suicide, 228 to cerebral hemorrhage, 245 to nervous and mental diseases other than general paresis, 503 to general paresis, 667 to diseases of the spinal cord, and 680 due to aneurysm. The total number of cases of tabes and paresis per year varied between 1,521 and 1,675 for the period from 1933 to 1937 inclusive. The reason for the author's presentation of the above data is that the question comes up from time to time whether venereal diseases should continue to be included in sick insurance. He feels very strongly that they should.

A poll on medical treatment. Illinois Health Messenger, Springfield. July 1, 1939, 11: 99.

A representative of the American Social Hygiene Association, in the role of a venereally infected person, recently visited 956 drug stores. The druggists in 66 percent of the stores offered to diagnose and provide remedies for his alleged trouble. Another 28 percent offered to sell remedies but would not undertake a diagnosis. Similarly a representative interviewed 1,023 persons in pool rooms, on the streets and in other places, asking where they would suggest that he go for treatment. A drug store was recommended by 65 percent, while going to a physician was advised by only 32 percent.

The transitory nature of the symptoms of syphilis greatly favors the practice of self-treatment during the early and curable stage. Thus the confidence in drug store remedies arises. This situation probably explains why such a large proportion of the reported cases of syphilis are patients in the late stages of the disease. Of approximately 10,000 cases of syphilis reported

in down-State Illinois last year, fully two-thirds were in the late stages, and less than 10 percent of the reported cases were of patients in the primary or earliest stages of the disease.

Performance of marriage license law tests and the use of forms in laboratories approved for performing standard laboratory blood tests. Connecticut Health Bull., Hartford. May 1939, 53: 116.

The following tests have been approved by the Connecticut State Department of Health for marriage license law purposes provided each test is performed in strict accordance with the latest edition of the Approved Method in a laboratory holding an unexpired certificate for performing the particular test: (1) Standard Connecticut complement fixation test; (2) Standard Kolmer complement fixation test; (3) Standard Eagle complement fixation test; (4) Standard Kahn diagnostic test; (5) Standard Kline diagnostic test; (6) Standard Hinton flocculation test; (7) Standard Eagle flocculation test. Any departure from the standard method is considered a modification of the test.

The State department of health has approved of the use of the Kahn presumptive test or the Kline exclusion test provided that (1) the latest edition of the Approved Method is followed and (2) any specimen giving any positive reaction shall be further subjected to and reported by one or more standard tests which the laboratory has permission to perform. These "exclusion" or "screen" tests are considered satisfactory for reporting marriage license law tests only when results are frankly negative.

Standard laboratory blood tests under the marriage license law are to be reported to no one but physicians holding a Connecticut license to practice medicine, surgery, or osteopathy.

Full information is given relative to the execution of forms used in connection with the marriage license law.

Venereal disease legislation. New laws require prenatal and premarital tests. Weekly Bull. California State Department of Public Health, Sacramento Mar. 25, 1939 and May 27, 1939, 18: 369.

On May 9, 1939, Governor Olson of California signed a bill requiring prenatal tests for syphilis, and on June 1, 1939, the Governor signed the bill requiring premarital tests for syphilis. Both the laws become effective 90 days after adjournment of the legislature.

The prenatal law provides that every licensed physician and surgeon or other person engaged in the prenatal care of a pregnant woman or attending such woman at the time of delivery shall obtain or cause to be obtained a blood specimen of that pregnant or recently delivered woman, at the time of the first professional visit or within 10 days thereafter. The blood specimen thus obtained shall be submitted to an approved laboratory for a standard serodiagnostic test for syphilis. Reports of the results of such tests shall be forwarded by the laboratory to the physician and duplicate reports shall be forwarded to the California State Department of Public Health. A third copy of such a report shall be retained by the laboratory and shall be open for inspection at any time by an authorized representative of the California State Department of Public Health.

The premarital examination law requires that before a marriage license is issued, each applicant must present a certificate from a physician stating that an examination (including a standard serologic test) has been made not more than 30 days prior to the date of issuance of the license, and that, in the opinion of the physician, the applicant is either not infected with syphilis or, if so infected, is not in a stage of the disease which may become communicable to the marital partner. The laboratory report shall be sent to the physician, a duplicate shall be sent to the California State Department of Public Health, and a triplicate shall be kept in the files.

he laboratory and must be available or inspection by any authorized representative of the California State Department of Public Health.

The sum of \$20,000 was appropriated for the expenses of administration of the law during the fiscal years 1939-40 and 1940-41. All claims against the appropriation shall be submitted for approval and audit to the California State Department of Public Health.

Incidence of syphilis in Puerto Rico.

Based on a review of 1,000 consecutive autopsies. Preliminary report. Enrique Koppisch. Puerto Rico Health Bull., San Juan. May 1939, 3: 197.

The author presents a review of 1,000 consecutive autopsies in the records of the Department of Pathology of the School of Tropical Medicine in San Juan. It was discovered that 81 (8.1 percent) showed anatomic evidences of syphilitic infection. In addition, 243 had a record of a blood Wassermann or Kahn test made upon admission to the hospital. In 34 of this group (13.9 percent of the 243 cases) one or another of these tests had been positive and 209 negative. There were, thus, 676 cases presenting no anatomic traces of syphilitic infection and having no record of serologic tests for syphilis. On the basis of the incidence of positive tests in the boye group of 243 necropsies, 94 additional cases would presumably have been found positive had the tests been made or recorded.

Thus, the total incidence of syphilis in the group of 1,000, estimated by adding together the cases with anatomic evidences, those with positive serologic tests, and those with presumably positive tests, was 20.9 percent. This figure is considered to be too high to apply to the general population of Puerto Rico but seems more truly representative of the incidence among the urban population of the Island.

In the series, syphilis was found twice as often in males as in females and somewhat less than twice as often in Negroes than in white persons. Anatomic

evidence of the disease was most frequent in persons 45 to 64 years of age. The cardiovascular system was affected in 77.7 percent of all cases of organic syphilis found, while involvement of the central nervous system was the principal manifestation in only 9.8 percent. Aneurysm was found in 33.3 percent of all cases with cardiovascular syphilis. Syphilis was the cause of death in 4.4 percent of the 1,000 patients coming to autopsy.

Results of contact investigation in syphilis in an urban community. T. B. Turner, A. Gelperin and J. R. Enright. Am. J. Pub. Health, New York. July 1939, 29: 768.

The material on which this report is based comprises 247 patients with primary and secondary syphilis admitted consecutively to the syphilis clinic of the Johns Hopkins Hospital between Sept. 1, 1936 and June 30, 1938. Only patients who applied voluntarily for admission and who had received no treatment prior to admission are included in the study. Patients with primary and secondary syphilis were considered "infectious cases" on the assumption that they were potential sources of infection in the community. Most of the original patients resided within the city limits of Baltimore.

In this series contact investigation is credited with bringing under treatment 114 previously unrecognized cases of syphilis. This is a ratio of 46 contact cases to 100 original cases. Of the contacts examined, 74 had primary or secondary syphilis and were potential sources of infection in the community. The ratio of infectious contact cases to original cases was 30:100. Approximately one-fourth of the contacts were under treatment for syphilis by some agency at the time the original case was admitted to the clinic. About one-fourth of the contacts examined did not have syphilis.

There was no significant difference in the results of contact investigation between white and colored patients or be-

tween male and female patients, but 11.1 percent of the marital contacts were non-syphilitic compared with 30.5 percent of the nonfamilial contacts. In a series of 87 original cases comprising young colored adults with latent syphilis, contact investigation yielded 3 previously unrecognized infectious cases and 11 other cases of syphilis. An estimate of the cost of contact investigation in this series shows that each previously unrecognized case of syphilis brought under medical care cost approximately \$10, and each infectious case cost about \$18.

Welfare Council of New York City, section on care of seamen. Annual report, May 1938-May 1939. (Mimeographed.)

The Welfare Council of New York City, section on care of seamen, adopted the general topic of health and recreation for its discussions during 1938-1939, and the majority of its activities centered around these topics. It has cooperated with the department of health in furthering the elimination and control of venereal diseases in the following ways: (a) using the facilities offered by the social hygiene department of the city board of health for publicizing methods of treating and controlling venereal diseases, (b) putting up suitable signs in the washrooms of the institutes, (c) seeing that information about venereal disease was included in the literature to be found in the libraries of the institutes, (d) seeing that individual cases coming to the attention of the institutes were referred to the proper clinics for treatment, (e) seeing that suitable recreation on shore was provided for men, particularly those with venereal disease, (f) instructing individual men on the necessity of taking treatment for venereal disease and not stopping treatment without the advice of the doctor, (g) cooperating with the marine hospitals in their care of cases to the end that the patients finish treatment. A report from the agencies indicated some progress in this program. An attempt was made to find

out how the steamship companies treat men infected with venereal disease and to secure their cooperation with the board of health in preventing and controlling it, but no results have so far been obtained.

A small committee is still experimenting with methods of referral of discharged patients from the marine hospitals.

The prevention of syphilis in marriage
Health News, Albany. May 22, 1939
16:82.

Sixteen States (at the time of writing this article) have premarital laws requiring a physical examination, including a blood test for syphilis, of both bride and groom. Vermont has discouraged nonresident marriages to avoid serologic tests for syphilis by making the clerk subject to a fine for issuing a license if he knows that the parties are barred from marriage by the laws of their State of residence. The Rhode Island law provides that residents married in other States who return to live in Rhode Island within 6 months of the marriage must submit to a physical examination including blood test. Persons with syphilis who marry outside of Wisconsin to avoid the State marriage law and later reside in the State without filing a certificate may be prosecuted under the public health law.

These marriage laws have been in effect too short a time to determine their value in preventing new syphilis infections or their effect on the number of marriages. However, a survey of 6 States suggests that marriages at first decreased but in a few months began to increase in number; that despite their inconvenience and cost the laws have gained public approval and are of value in educating and in preventing the spread of syphilis in marriage. Of 227,537 premarital blood tests made in 5 States, 1.5 percent were positive. Two tables are given showing the variation in the total number of marriages and the experience with serologic tests in certain States having premarital laws.

Medical examination required for marriages performed in Ciudad Juárez, Mexico. Typewritten memorandum from American Consul General. June 30, 1939.

Beginning July 1, 1939, all applicants for marriage licenses in Ciudad Juárez, Mexico, must undergo a physical examination and present a certificate of good health before licenses may be issued to them. Previously, medical certificates were required only in cases where one of the applicants appeared to be suffering from some disease. The present requirement has been ordered by the Federal Department of Health, Mexico.

The medical certificates may be obtained, without charge, from certain doctors designated by the government. The physical examination will include a Wassermann test. The opportunity of obtaining a free medical certificate will, according to the Judge of the Civil Register, do away with the possibility of graft and the obtaining of false certificates for monetary considerations. However, when applicants are not residents of Ciudad Juárez, he will accept a medical certificate from some other reputable doctor.

The prostitution "racket"; related health problems; and a suggested remedy.

Bascom Johnson. J. Soc. Hyg., New York. May 1939, 25: 209.

It is a recognized fact that prostitution is an important reservoir of syphilis and gonorrhea and that this reservoir will increase in size and power in any community which fails to do something to dry it up. Some believe that prostitution can be made and kept sanitary under a system of licensing or toleration. The police and other official agencies generally look upon prostitution as either a perennial headache or as a source of profit. Some of them advocate the licensing of prostitution; they say that this would increase revenue to the city and release police for other necessary duties. If license fees were high enough to produce real revenue, bootleg prostitution would be encouraged. The license system has proved a failure in the Euro-

pean countries where it has been tried. It has been the experience of communities that have tried the license system that it is easier to bribe the police under this system than under a system of repression by law. There is no point at which the license system has broken down more completely than in its effort to make prostitution sanitary. Examinations thorough enough to detect disease have been found utterly impracticable; no public health department advocates such a policy. Health departments are generally loath to tackle the problem of prostitution, holding, rightfully, that it belongs in the police departments and in the courts.

The net results of all these differences of opinion and divided responsibilities are inefficiency and regression. To meet the situation squarely it must be recognized that a civilian emergency exists. To meet the emergency certain principles have been tried out in several cities with resulting improvement in conditions. (1) Education of the young men in the necessity and practicability of self-control. (2) Law enforcement aimed at the racketeers, the procurers, the promoters, and the exploiters; with these persons eliminated prostitution becomes a manageable affair. (3) The protection of public health by handling diseased prostitutes in exactly the same way as their diseased customers; all should be required to take treatment and to refrain from exposing others to their infections.

Johnson outlines a plan for what he calls an unofficial "grand jury" investigation of prostitution in a community. This jury, composed of citizens representing all classes and professions, should be appointed by some unofficial organization but should have the approval of the community's officials if possible. It would not have the legal rights of an official grand jury in demanding witnesses and testimonials, but this has not proved to be detrimental. Johnson assisted in such an investigation as a representative of the American Social Hygiene Association which,

together with the U. S. Public Health Service, was called upon to participate in a study of the conditions in a city with a population of approximately 250,000. This investigation was instigated by the president of the local chamber of commerce, which wanted to know why their city stood so low in the nation's health list. The report of the unofficial grand jury in this city was never published. It was never necessary to do so. The knowledge of its existence proved sufficient to secure remedial action in regard to the most flagrant conditions. As a mechanism by which the community could study and evaluate its own social conditions, it received the hearty approval of the community.

Interesting findings from premarital blood examinations. Quart. Bull. City New York Dept. Health. May 1939, 7: 25.

A compilation and analysis of the tests made for syphilis in New York City during the 6 months between July 1, 1938, when the law providing for blood tests of all applicants for marriage licenses became effective, and December 31, 1938 yields some interesting information.

Premarital blood tests were made on 58,903 individuals in New York City and 0.95 percent were positive for syphilis. Only 6,412 of these tests were made by private laboratories. Of the tests done by the health department, 1.03 percent were positive, and by the private laboratories only 0.27 percent. Of the 52,167 persons whose color was stated as white, 0.61 percent were positive and of the 2,444 Negroes, 9.82 percent; there were 4,386 whose race was not stated. If half of this latter group were added to the Negroes it would bring the minimum percentage of positive Wassermanns among the Negroes to 5.18 percent. Of the total 559 persons who had positive reactions 319 were male and 240 female.

The low incidence, 0.95 percent, of syphilitic infection may be influenced by the fact that persons knowing them-

selves to be infected will be less likely to apply for a marriage license requiring a blood test. On the other hand the group is made up entirely of people of marriageable age, and the one-fifth of the city's population who are under 15 years of age has a very low incidence of syphilis. The writer believes that a rate of not over 1 percent will represent the incidence of syphilis for New York City and he wonders if the work of Doctor Hermann M. Biggs, which was put in operation in 1912 and has been continued for 25 years, cannot reasonably be expected to have brought about this low incidence.

Venereal disease control in the U. S. S. R. News from other countries. J. Soc. Hyg., New York. May 1938, 25: 251.

The campaign against venereal diseases in U. S. S. R. is carried on by the Government by means of free treatment of infected persons and by educational activities. Since the October 1917 revolution the incidence of venereal diseases has decreased considerably; in some districts it is only $\frac{1}{4}$ and in others as low as $\frac{1}{20}$ of that in 1917. In Leningrad only 2.75 cases per 10,000 population were registered in May 1938, as compared with 5.5 cases in the same month in 1937. A similar decrease has been noted in the incidence of gonorrhea while chancroid has been almost completely eradicated.

Recently a compulsory Wassermann blood test has been introduced for prenatal cases. For the first few months of this year there were only occasional single cases reported for each 10,000 prenatal examinations.

That the incidence of syphilis is diminishing among adolescents is shown by the fact that among those who answered the Red Army call only few districts out of 28 had several cases of syphilis. Eight districts reported no single case.

The Public Commissariat of Health Preservation disseminates information regarding hygiene in general and hygiene in particular. The Institute of Sanitary Culture supervises the meth-

f teaching which is extended to the young people in colleges, vocational, and professional schools.

Sweden vs. our shadowed land. Helen Clarke. J. Soc. Hyg., New York. May 1939, 25: 221.

Becoming much interested in the problem of the control of venereal diseases in Sweden after reading "Shadow on the Land," the author planned a visit to one of the venereal disease clinics when she revisited Sweden. The polyclinic at St. Görans Hospital in Stockholm is very easily reached by street car or bus, and clinics are held 6 days a week with both morning and evening sessions. This is the only hospital in the city where venereal disease clinics are held. Men and women are admitted to their separate divisions through entrances at opposite ends of the building. There are pew-like seats in the large light waiting rooms. Between these rooms and treatment offices is a light dressing room with curtained booths.

Doctor Gerda Kjellberg is the chief of the woman's division and has had 26 years of distinguished service. She stated that Sweden did not have many new cases of syphilis—the rate in Stockholm for 1937 was 1.2 per 1,000 inhabitants. Rietz summarized the basis for Swedish legislation against venereal disease as being "Search for and detection of the source of infection as in other contagious diseases."

When a diagnosis of venereal disease is made, the physician must inform the patient of the type of infection and the dangers of transmission. He is given a 7-page pamphlet containing directions to prevent spreading the disease, and he is told that the law forbids his marriage or subjecting another person to infection. It is the duty of the physician making the diagnosis to trace the source of infection, and a printed order is sent to this person to report for treatment. If he fails to report for treatment he is notified by a printed form, and if this fails to bring him in he is subject to compulsory treatment which would mean hospitalization.

Treatment is compulsory and free, and the drug therapy is much the same as in the United States.

While not everything in Sweden is perfect, Doctor Kjellberg stresses the fact that the treatment given the patients is good.

The writer left the clinic with a feeling of gratefulness that Sweden is doing her best for unfortunate sufferers by treating them as communicable disease cases. The afflicted know the necessity for rational treatment and with the law behind them the physicians can give it consistently and continuously.

The need for V. D. propaganda. J. H. F. Pankhurst. Med. Officer, London. June 17, 1939, 61: 241.

There is little need to emphasize, Pankhurst says, that the cost to the nation of untreated venereal disease both in life and in money is immense. The advantages of preventive methods and early treatment are measurable in a tangible form. The untreated syphilitic is predestined from the commencement of infection to the probability of a lifetime of ill health, the infection is carried to the marital partner and transmitted to the children, and eventually a whole family may need to be maintained in public institutions. The consequences of untreated gonorrhea are less severe but only in degree. A policy of offering early and complete opportunities for cure free to every victim of venereal disease is in the interest of the State as much, if not more, than of the individual.

Justification of such public schemes may be necessary especially in rural communities unused to free discussion of venereal disease problems. The public conscience is slow to grasp that venereal disease is not always connected with vice or that the standard of sexual morality is much below that set as an ideal. Much has been achieved in England and other countries where enlightened public opinion has allowed competent schemes to be evolved. Future progress will tend undoubtedly in the direction of strengthening existing methods and in encouraging the dissemination

tion of propaganda. In this connection the press has a great mission to fulfill, Pankhurst believes. The British Social Hygiene Council is doing a great amount of good in spreading knowledge of venereal diseases and how they can be cured and eradicated. The most potent weapon against venereal diseases is an educated and enlightened public opinion.

The school's responsibility to the home and the child in sex education. W. Linwood Chase. Bull. Massachusetts Soc. for Social Hyg., Boston. June 1939, 9: 8.

The amount of reliable and scientific knowledge now available in carefully prepared publications and the detailed suggestions that have been made for putting into effect a program of sex education are far in advance of the skill and understanding available among adults (parents, teachers, and other workers with children) who are called upon to give information, to guide and direct the sex strivings of children and youth. Filled with inhibitions about sex as many adults still are, their emotions will not allow them to carry out what their intelligence tells them they should do.

In the past 15 years there has been much activity in the field of character education in the public schools. Though, on logical grounds, sex education should be inherent in every program of character education, few such programs include the subject.

Sex education is a continuing process from the earliest years of the first sex question to the later years of complete understanding. Many boys need the sex actions and talk of other boys interpreted to them in order to build the proper attitudes. Discussions concerning the subject should not be furtive and secretive, yet premature exploration should not be encouraged. Sex curiosity should be satisfied at the level where it has developed in the child and future levels to which the curiosity is approaching should be anticipated, yet higher levels of such curiosity should not be prematurely satisfied. Sex should not

be considered a problem but a normal aspect of a normal life. The development of sex adaptations and attitudes varies as widely in different persons as do mental and physical growth.

Some of the reasons why sex education cannot be left entirely to the home are as follows: (1) The school has many more opportunities for presenting accurate information, (2) parents have a tendency to underestimate the sex maturity of their children, (3) many parents are so poorly informed themselves that they cannot offer any worthwhile guidance. Too much of sex education that has been carried on by parents has concerned what the child must not do.

Teachers must be able to discuss sex without over-emphasis, must not be shocked by what may be discovered in personal conference, and must view sex education as a part of the larger process of character development.

The author describes his own experiences in presenting the subject of sex to the boys of a private school. The fact that some sex education is included in nearly every subject studied is emphasized. The best work of a school in sex education can be done almost wholly through the work of the entire teaching staff in all their contacts with boys: in the classroom, at the dinner table (in a private school), and on the play field. The subject of sex should not be limited to discussion in a single course. There is a tendency to place an abnormal emphasis upon a perfectly normal matter.

Personal discussions on the subject are valuable because they give the adviser a key to the inner emotional life of the child. The boy thinks that, since he has been able to talk about such intimate things, there is nothing that he cannot discuss with the adviser. The rapport is established or strengthened.

The private school study. George Northrup. Bull. Massachusetts Soc. for Social Hyg., Boston. June 1939: 5.

The Massachusetts Society for Social Hygiene has sponsored jointly with the New England Health Education As-

iation a study on sex education in 41 private schools in the vicinity of Boston. A fair sample of grade and age levels and school situations was obtained, including lower grades in both boys' and girls' schools, coeducational schools, "progressive" schools, and college preparatory schools.

It was desired to determine the best methods for presenting sex education and to discover the reactions and responses of pupils, parents, and teachers. A personal interview was obtained with members of the school staffs and questions were asked about "integrated" sex instruction and specific sex instruction offered in the schools. "Integrated" sex instruction includes all material given within the subject matter of a course which may directly or indirectly assist the pupil in understanding the meaning of sex. Specific sex instruction includes instruction given directly on the subject of sex.

The majority of the schools studied accepted the fact that they have a definite responsibility to the home and the child in giving sex instruction and were willing to take steps to meet the situation. The parents, when they were aware of what the schools were doing, were usually in favor of the program.

It was agreed that sex education should accomplish the following ends:

(1) Satisfaction of natural curiosity, (2) the acquisition of a correct vocabulary, (3) proper integration of sex with all life's processes, (4) removal of undue emphasis on sex which results from its present omission and exclusion from general discussion both in the home and in the school, (5) provision of a background for a better understanding of emotional problems when they arise. Sex education will probably not obviate all sex tension or prevent the mishandling of the sex urge, but it is of value in counteracting misinformation.

This study is not sufficiently extensive to indicate more than tendencies and trends in the field of sex education and should be considered only a guide for further study. It is planned to continue the investigation to study (1) the trend

of sexual thinking on the part of children in the pre-adolescent and early adolescent periods, (2) the background and attitudes of the teachers and counsellors in the schools to determine the probable impression left upon the child as a result of his contact with these adults, (3) the type of sex education now being given in various schools throughout the country, (4) the advisability of establishing a teacher-training course in sex education for teachers in service, (5) the extent of sex education in graduate schools of education.

Physicians' fees for taking premarital blood specimens. New Hampshire Health News, Concord. June 1939, 17: 6.

The committee on public relations of the New Hampshire Medical Society has asked all members of the society to charge only a moderate fee for taking the premarital blood sample, making the physical examination, and issuing and signing the premarital certificate. The committee believes that this fee might well be the regular fee for one office visit. Except in unusual cases, they believe the fee should not exceed three dollars.

Let there be light. Illinois Health Messenger, Springfield. July 1, 1939, 11: 100.

Illinois began to distribute silver nitrate solution free of local cost in 1914 and the use of an approved prophylactic in the eyes of new-born babies was made compulsory by law in 1933. The department of public health distributes the silver nitrate solution free and the Illinois Society for Prevention of Blindness scans every birth certificate for a record of whether or not a prophylactic was used. There are noteworthy results from the 25 years of effort in this work. No case of blindness from ophthalmia neonatorum has occurred in this State since 1936. The enrollment in the School for the Blind in 1920 was 215, or a rate of 33 per 1,000,000 inhabitants in the State; in 1939 it was 237, or a rate of 30, although the population in the State hospitals doubled in that time.

Incidentally, the department of public health manufactures both the silver nitrate solution and the ampules which it uses. These ampules have recently been changed and do away with a chemical action in the old form of container which often caused a rather severe irritation of the eyes when the solution was used.

The case against prostitution. Editorial. J. Soc. Hyg., New York. May 1939, 25: 240.

Commercialized prostitution, for some years after the World War somewhat reduced by community effort, is at the present time a more threatening menace to American public health and welfare than at any time since the war days. It is more daring, more insidious. Nation-wide studies made by the American Social Hygiene Association during the past year indicate a definite slipping backward in many sections of the country. The indictment against this evil is clear; commercialized prostitution injures public health, strikes at the home and family, exploits young people, encourages sex delinquency, and increases graft. Prostitution as a "racket" involving bribery, intimidation, and extortion can and must be suppressed. Prostitution as a "business" including the recruitment and ruthless exploitation of thousands of new girls every year can and should be made so difficult, hazardous, and unprofitable by law enforcement that it will die.

The American Social Hygiene Association is steadily attacking prostitution through surveys, stimulation of law enforcement activities, and education of youth. Wilbur, President of the Association, has recently made an appeal for special contributions to be used for the campaign against commercialized prostitution.

The Wassermann surveys. Editorial. Med. Rec., New York. June 21, 1939, 149: 396.

The prevalence of syphilis in the population varies with age, race, and economic status, and it is difficult to de-

termine its extent by any one set of statistics. During recent years Wassermann test surveys have been made among many groups of persons. If it were possible to have weighted statistical averages, these surveys would give a fairly good estimate of the prevalence of syphilis. On the basis of such statistical surveys, the figures of 5 to 10 percent of the population have been used to indicate the extent of the syphilis problem in the United States.

Recently a group of New York City lying-in hospitals reported the results of serologic tests of women who sought admission. Serologic evidence of syphilis was present in 8.5 percent of the women. Results of a survey at a New York Hospital for diseases of the skin showed that about 4 percent of the patients seeking admission had syphilis. A survey of insane patients in New York State revealed the fact that 10 percent were syphilitic. About half the women at Bedford Reformatory in New York were found to be syphilitic.

However, only 0.6 percent of a group of prospective white blood donors in New York City had positive Wassermann tests. The reason for this low prevalence has probably been that many persons seeking blood donor status had probably had preliminary unofficial examinations prior to the one given by health authorities. Those persons with any physical defects (including positive serologic tests) did not appear for official examination.

A similar situation probably exists in the matter of premarital blood tests. Physicians and others are known to have called the health department laboratory by telephone and asked to have a negative Wassermann result transferred from the ordinary report form to a premarital report form. "Feeler" serologic examinations have undoubtedly been made in many cases. If such tests were positive, no efforts would be made to secure a premarital form within the State.

Persons from southern States and semitropical islands may sometimes have positive serologic tests (and no other

symptoms of syphilis) because of the effects of previous infections with such diseases as malaria or yaws.

In New York, the premarital law provides for possible errors in interpretation of the serologic report by requiring the physician, not the laboratory technician, to make the final decision. Persons with positive Wassermann reactions without evidence of the presence of syphilis in a communicable form may secure the certificate enabling them to procure a marriage license.

The official premarital serologic results cannot be considered an indication of the extent of syphilis infection in the general population.

Syphilis control. Administrative and epidemiologic aspects. Cleland A. Sargent. New York State J. Med., Albany. May 15, 1939, 39: 1011.

Sargent says a syphilis control program should include case-finding, location of sources of infection by epidemiologic investigation, treatment of patients with early and potentially infectious syphilis, prevention of congenital syphilis, statistical studies, and public health education. He discusses these topics largely in relation to the work at Buffalo. He emphasizes the advantages of a syphilis register in which the case cards are completely filled out and filed whether negative or positive. There are many ways that the information obtainable from them is useful. Every precaution should be taken to keep the information confidential, and no reports should be given over the telephone even to the attending physician.

Compulsion should not be used to obtain the examination of contacts. The investigators should not be permitted to interview a patient in the presence of another individual. In an investigation of 810 cases of early syphilis, 611 contacts were named; 33 were reported by first name only, and inmates of 39 houses of prostitution were designated. Twelve contacts refused to be examined,

and serologic tests were positive for 336 resident contacts. In the author's experience it has been necessary to investigate approximately 9 early infectious syphilis cases to find 1 early case not previously reported among the contacts. It was found that the average cost of investigation of early syphilis was approximately \$7.00 per case, and the average cost of locating and persuading contacts to submit to examinations was approximately \$17.00 per contact.

A recent study of the treatment histories of 666 cases of early and potentially infectious syphilis showed that 50.3 percent of private cases and 75.5 percent of clinic cases lapsed treatment before 40 doses of antisyphilitic drugs were administered, and there was an average of 1.6 lapses per patient. The nurses made an average of 3.6 visits per lapsed case.

In Buffalo the names of all applicants for marriage licenses are checked against the syphilis and serologic registers. All pregnant women who have been infected with syphilis are visited by the nurses. The names of all married and unmarried mothers of babies born in the city during January 1938 were checked against the syphilis and serologic registers and only 8 percent had had serologic tests during pregnancy.

The medical staffs of industrial plants are being urged to consider each case of syphilis among their employees or prospective employees individually and to employ those persons who will cooperate by submitting to regular treatment.

Recently 175,000 letters to residents of Buffalo have been sent out. To obtain an active mailing list and to avoid the criticism of using the names on the syphilis register, a large commercial firm of the city was induced to use its mailing list and to address the mail in its plant.

A department with a small staff may not be able to conduct a case-finding and epidemiologic investigation program, yet a program of keeping infectious cases of syphilis under treatment should be a part of every public health department.

LABORATORY RESEARCH

Studies on the excretion of sulfanilamide by the digestive glands. Haddon M. Carryer and A. C. Ivy. *J. Pharmacol. & Exper. Therap.*, Baltimore. July 1939, 66: 302.

From their study of the excretion of sulfanilamide in the digestive juices and its effect in therapeutic doses on the secretory activity of the liver of the dog, the authors make the following deductions:

Sulfanilamide is excreted in the bile, pancreatic juice, gastric juice, succus entericus, and saliva of the dog in appreciable quantities. Levels of sulfanilamide that are thought to be bacteriostatic may be attained in the hepatic bile. Sulfanilamide was not definitely toxic to the liver in doses of from 0.66 to 1.3 grams orally per day for 3 days in dogs weighing 7 to 12 kilograms. The trend is toward decreased cholic acid and increased pigment output. The concentration of sulfanilamide in pancreatic juice roughly parallels, but is less than, the concentration in the blood.

The highest concentration was obtained in the gastric juice. It may be as high as 50 mg. per 100 cc. of gastric juice at 4 to 6 hours after the oral administration of 2 grams of the drug to dogs weighing from 8 to 13 kilograms. Excretion of sulfanilamide in gastric juice with blood levels as low as 2.2 mg. per 100 cc. was demonstrated.

Concentration of sulfanilamide in human bile. R. Bettman and E. Spier. *Proc. Soc. Exper. Biol. & Med.*, Utica. June 1939, 41: 463.

Eleven patients who were to be operated on for gall stones were given sulfanilamide before operation and speci-

mens of the bile and blood were taken at the operation. The study of the specimens showed that sulfanilamide is excreted in the bile and that it may be concentrated considerably in the gall bladder.

Experimental study of the effect of the protein fraction and the dialysate of syphilitic serum in the Wassermann reaction. Carlo Scaglioni. *Pathologica*, Genova. May 1939, 31: 190.

The author describes experiments which he carried out for the purpose of determining what part of the serum brings about the positive Wassermann reaction in syphilis. For the purpose of determining whether the Wassermann substance is free in the serum or bound to the protein he dialyzed serum through collodion membranes of gradually increasing density, so that the protein content of the dialysate gradually decreased. He describes the technique of the experiments and gives tables showing the details of the results. He found that the positiveness of the serum increases in proportion to the completeness of the removal of the proteins from it and concludes therefore that the Wassermann substance is contained in the proteins. A dialysate from which the protein was completely removed always gave negative reactions.

By further experiments he found that the only protein fraction that gives a positive Wassermann reaction is the one precipitable by ammonium sulfate. This fraction, which contains the serum globulin, gives the same kind of Wassermann reaction as that of the serum from which it is derived. There is no specific change in the Wassermann reaction of the homologous serum or its serum albumin or the serum globulin or serum albumin of a normal serum is added to this fraction, but there is an increase in the degree of positiveness of the reaction of the dialysate, freed of protein substances, of a syphilitic or nonsyphilitic serum is added to this fraction.

studies on the question of preservation of biologic qualities of serum, with particular reference to complement. A contribution to the theory and application of the complement-fixation reaction. A. Germershausen. Ztschr. f. Immunitätsforsch. u. exper. Therap., Jena. June 26, 1939, 96: 1.

The various methods which have been used for the purpose of preserving complement, including addition of glycerin (Graetz, 1910), addition of boric acid and sodium chloride (Kalinin and Ginsburg), freezing (Morgenroth, 1904, who used a specially constructed "ice-box"), carbon dioxide snow (Loeffler and Kranich) drying (Friedberger, 1908) are discussed in detail with reference to the literature. The disadvantages of each method are pointed out. The author has interested himself particularly in the method first advocated by Kalinin and Ginsburg, which was also critically tested by Sonnenschein, consisting of adding boric acid and sodium chloride to serum for the purpose of preserving complement. He also tried boric acid and sodium acetate. On the basis of purely experimental studies as well as of practical application, he recommends the boric acid-sodium chloride method as the method of choice but also states that the method of adding boric acid and sodium acetate has been of practical value. By means of adding boric acid and sodium chloride, guinea pig serum complement can be preserved for 3 to 6 months without loss of potency. There is no more difference between complement preserved in this manner and fresh complement than there is between two samples of fresh complement. This method of preservation is not limited to preservation of guinea pig complement but can also be used to preserve other qualities of serum, such as amboceptors and agglutinins.

The influence of different gonococcus antigens on the result of the complement fixation reaction with the serum of patients with gonorrhea. K. W. Jötten and M. Frese. Ztschr. f. Immunitätsforsch. u. exper. Therap., Jena. July 11, 1939, 96: 172.

On a total of 222 serums which had been obtained from definite and from doubtful cases of gonorrhea the gonorrhea complement fixation reaction was carried out with 3 polyvalent antigens, namely "compligon," "labopharma" and "behring." Preliminary complement fixation reactions with these antigens and the serums of patients with syphilis and tuberculosis but who were definitely free from gonorrhea were carried out to avoid nonspecific complement fixation reactions for gonorrhea. It was found that 45 (20.4 percent) of the 222 serums gave a 3 to 4 plus reaction with all 3 antigens, 32 (14.4 percent) gave a 1 plus or plus-minus reaction, 78 (35 percent) were negative, and indefinite results were obtained in 67 (30.2 percent). Therefore a total of 155 serums showed agreement with all 3 antigens, whereas 67 serums gave indefinite, variable results. It was found in further studies with polyvalent and with monovalent antigens (commercial as well as some prepared by the authors) that these variable results can be attributed to variations in the preparation of the antigen and to the different antigen character of the gonococci which are used in the preparation of antigen. As was expected, more negative results were obtained with the monovalent antigens. It is important that in the preparation of polyvalent antigens different gonococcus-type groups are included.

Lowered resistance to syphilitic infection in ovariectomized rabbits. C. K. Hu. Am. J. Syph., Gonorr. & Ven. Dis., St. Louis. July 1939, 23: 446.

It is agreed generally that syphilitic infection, in experimental animals as well as in man, runs a milder course in

the female than in the male. It has been observed that the administration to male rabbits of an estrogenic substance, extracted with butyl alcohol from the urine of pregnant women, renders the course of syphilis milder than that in untreated animals.

The author reports the results of a study made of the effect of ovariectomy on the course of syphilitic infection in the rabbit. The operation was performed on rabbits of various ages, and these animals were inoculated with syphilis at various intervals of time following the operation. Both intracutaneous and intravenous routes of inoculation were used. A total of 92 rabbits survived long enough to be included in the analysis of the results.

It was found that the removal of the ovaries caused the syphilitic infection in the rabbit to run a more severe course than in animals with ovaries intact, although the effect was brought out significantly only by inoculating a large dose of virus intravenously. It is thought that the primary female sex hormone exerts an inhibitory influence on the course of the infection but that it alone is not responsible for all the difference in severity of the infection between the two sexes.

The effect of testosterone propionate on the course of experimental rabbit syphilis. Jarold E. Kemp, Clarence Shaw and Elsie Mae Fitzgerald. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis, July 1939, 23:430.

In a study of the effect of the male sex hormones upon the course of experimental rabbit syphilis, 5 mg. of testosterone propionate was administered intramuscularly to 42 rabbits for 4 weeks before and 8 weeks after inoculation with the Nichols strain of *Treponema pallidum*. The animals included in the experiment were divided into 5 groups: (1) Castrated males treated with testosterone, (2) normal males treated with testosterone, (3) normal females treated with testosterone, (4) untreated males, (5) normal untreated females. Seventy-one animals,

divided approximately equally between the experimental and control groups survived the experiment.

It was found that the course of syphilitic infection was milder in both control and experimental groups in this experiment than in previous experiments, probably because of the mild weather which prevailed during the winter that it was in progress. That non-castrated males treated with testosterone reacted more severely to infection than normal untreated males was indicated by the fact that the maximum size of the chancres which developed at the site of inoculation in the former group was 35.3 by 28.6 mm. and generalized lesions developed in 92.3 percent of the group. In normal untreated males the average maximum size of the chancres was 32.6 by 24.8 mm. and generalized lesions developed in 73.3 percent of the group.

The reaction to infection of castrate males treated with testosterone and of normal males and normal females was approximately the same. There was little difference in the average maximum size of the primary lesions in these groups (treated castrated males—28.1 by 21.6 mm., normal males—32.6 by 24.8 mm., normal females—32.6 by 24.8 mm.) The incidence of generalized lesions, excluding testicular and scrotal metastases found in normal males, was about the same (treated castrated males—23.1 percent, normal males—33.3 percent, normal females—23.1 percent). Treated female rabbits reacted less severely than any of the experimental or control groups since none of them showed evidence of generalization. Excluding testicular metastases, 33.3 percent of the male control animals showed evidence of generalization, and 21.4 percent of the female control animals showed such evidence.

It was thought that the male sex hormone (testosterone propionate) would enhance the course of syphilitic infection in male rabbits in comparison with the course in untreated control animals and make the infection equally

vere in treated castrated male, treated normal female, and untreated male rabbits. While these assumptions were partially confirmed, the difference in the behavior of the various experimental and control groups was not sufficient to permit definite or final conclusions from the results. The authors believe that research in the effect of male and female sex hormones on experimental syphilis must await more exact knowledge of their inter-relationship in both man and the experimental animal that is employed.

PATHOLOGY

Congenital neurosyphilis. Report of a case with unusual encephalographic changes. G. M. Wyatt and B. W. Carey, Jr. *Am. J. Roentgenol.*, Springfield. May 1939, 41:779.

The patient, a white infant 10 weeks of age, was admitted with the complaints of "holding the head back" and "snuffles" of 8 weeks' duration. She was the first child of parents who denied syphilitic infection although subsequent tests showed both parents to have a positive blood Hinton test. The child lay in a marked opisthotonos position. There were papules distributed thickly over the back and dorsal surface of the legs. The anterior fontanelle was tense, the bridge of the nose depressed, and there was a profuse bloody nasal discharge. The blood Hinton test and cerebrospinal fluid Wassermann tests were positive. Roentgenograms showed changes in the long bones diagnostic of congenital syphilis. Therapy was started with a mercury binder, followed by two intramuscular injections of hypoloid bismuth and a course of 12 intravenous injections of mapharsen. Hypoloid bismuth was then resumed for 8 weeks, and 12 weekly injections of mapharsen. Following this the treatment to date has consisted of alternate courses of acetarsone and mercury injections for a total of four

courses. The opisthotonos did not disappear until 3 weeks after mapharsen was started.

The patient was readmitted to the hospital at the age of 6 months and encephalograms showed dilated lateral and third ventricles and deep wide cortical sulci. The blood Hinton and cerebrospinal Wassermann tests were positive. At the age of 18 months psychometric examination showed a mental development comparable to a normal infant of that age. There was a mild right hemiplegia. The cerebrospinal fluid was negative.

The authors consider the interesting points in this case to be (1) the survival of a patient with symptoms of such severity that the initial prognosis was considered hopeless, (2) the response to therapy with the relatively new arsenical, mapharsen, (3) the growth of brain tissue following apparent cortical atrophy as demonstrated by encephalography, (4) the surprising degree of mental and physical function which has resulted under continuous antisyphilitic therapy.

Chronic simple ulcer of the vulva. G. Marieonda. *Dermosifilografo*, Milano. Feb. 1939, 14:117.

The author reviews the literature in regard to chronic simple ulcer of the vulva or Clement Simon's disease and describes a case which he saw in a prostitute 45 years of age who had had syphilis. She had been castrated surgically. The differential diagnosis from various other conditions with which these ulcers may be confused is discussed. These include secondary manifestations of syphilis, superinfection and reinfection with syphilis, epithelioma, Lipschütz' acute ulcer of the vulva, soft chancre, tuberculous ulcer, gonorrheal ulcer, esthiomene, and tertiary syphilis.

Attention is called to the multiplicity of the ulcers around the opening of the vagina which is subjected to repeated trauma in prostitution. While a single ulcer at the fourchette is quite characteristic of this disease, the ulcer or ulcers may be located at other points but

always in the neighborhood of the vaginal opening. The relationship of these ulcers to esthiomene is very obscure; however, the author believes the chronic simple ulcer of Clement Simon can be differentiated from esthiomene and that it can be definitely shown that it is an independent disease. Its interest lies in its resemblance to syphilis and the difficulty in many cases of differential diagnosis.

Huge syphilitic aneurysm: Case report.

John H. Foster. J. Connecticut M. Soc., Hartford. June 1939, 3: 276.

A search of current literature and of textbooks has revealed no report of an aneurysm so large as this reported one.

A 59-year-old widow was first admitted to the Waterbury Hospital in 1934, complaining of cough and dyspnea of 5 months' duration, and pain in her right shoulder. The blood Wassermann was positive. She was discharged with a diagnosis of syphilitic heart disease, congestive heart failure, and aortic aneurysm. She was readmitted to the hospital twice and was under observation at the dispensary for more than a year. The mass had been growing steadily and was causing severe pain in the neck and right shoulder and affecting her speech and breathing on her final admission on Jan. 2, 1936. This tumor mass extended from the right shoulder blade to the left of the sternum and from the right submaxillary region to the third costal interspace. It measured about 17 cm. in each diameter and was raised about 6-7 cm. in the center. On Jan. 31 the measurements were 22 x 21 x 9.5 cm. On Feb. 17 several superficial erosions appeared on the surface, with some oozing of serum. On Feb. 25 blood spouted 4 or 5 feet out into the room from a pin-point opening; and then other small streams started. The bleeding continued for several hours when she became unconscious and expired 4 hours later. Autopsy was refused.

Venereal lymphogranuloma. Rigne D'Aunoy and Emmerich von Haam. Arch. Path., Chicago. June 1939, 27: 1032.

The authors' intensive study of venereal lymphogranuloma, extending now into its sixth year, has afforded them ample opportunity to become familiar with most of the problems presented by the disease and to make many important observations regarding its causal agent, clinical manifestations, and pathological character. They have correlated previous information, recorded the results of their more recent studies, and reviewed such important matters as the history of venereal lymphogranuloma, the geographic distribution and incidence, the clinical manifestations, the pathological lesions, the biologic characteristics of the causal agent, and the various methods of diagnosis and therapy in the very comprehensive review. They have also included a great many references to the literature in the bibliography.

Contribution to the question of tubercloid syphilids and the immunity of the scar of late syphilids. R. Bezean. Dermat. Wehnschr., Berlin. May 2, 1939, 108: 591.

In 7 cases of late syphilitic scars negative luetin test of the scar and positive test of the surrounding skin was obtained. In contrast to this the reactions of tuberculous lesion scars were positive to the tuberculin test. No syphilitic scars (following vaccination, burns, etc.) in patients with positive luetin tests reacted like the normal skin in that they also gave a positive reaction. Scars of syphilitic lesions gave positive tuberculin reaction in tuberculin-positive patients. The findings in one patient who had a tubercloid syphilid are presented in detail. In 19 this patient had a tubercloid syphilid on the dorsum of the right foot and squamous syphilids of the palms. The palmar syphilids healed with speci-

treatment but the lesion of the foot could partly heal and continuously break down again. The luetin reaction was positive in 1936, negative in 1937, and later became positive again. The blood test for syphilis which at first was negative later became positive. The histologic picture was that of a mixed infection of tuberculosis and syphilis. Tubercle bacilli were demonstrated culturally after a prolonged search. In this case the luetin reaction of the scar was positive, whereas it was negative in the normal skin, later becoming positive. The tuberculin reaction of the scar and of the normal skin was positive. The author states that the assumption that in many cases of tuberculoid syphilids are a mixed infection of syphilis and tuberculosis finds confirmation in this case.

A bullous eruption due to sulphanilamide. F. Ray Bettley and Philip Simon. Brit. M. J., London. June 10, 1939, 1: 1177.

The case is reported of a male patient with gonorrheal anterior urethritis on whom a bullous eruption occurred after treatment with sulfanilamide. For 3 days he took 1 gm. of the drug 4 times daily. Malaise and nausea resulted from the treatment and the dosage was then reduced to 1 gm. 3 times daily. The urethral discharge ceased 6 days later and did not reappear. Six days after the discharge disappeared there was slight edema of the hands and forearms with a faint morbilliform rash on their extensor surfaces. Treatment was continued and two days later the condition was unaltered. The patient then defaulted but continued to take the drug. A week after the edema and rash appeared he stopped work because of severe swelling and blueness of the face, forearms, and hands. Photophobia and malaise developed. He took no more sulfanilamide after this time. Two days later blisters appeared on the face, forearms, and hands. These gradually formed crusts. Twelve days after the blisters first appeared a fresh attack of swell-

ing and blister formation occurred. Six days after this second attack he reported for treatment again with a profuse bullous eruption on the face, neck, forearms, and hands, and a sparse eruption on the trunk. He was a gardener, and the parts on which the rash occurred were exactly those parts which were exposed to light with the exception of the few lesions on the trunk.

The author reviews the literature on rashes due to exposure to light following sulfanilamide therapy. Newman and Sharlit (1939) have suggested that there is either a direct light-sensitization caused by the drug, or sensitization is indirectly due to the drug by the production of porphyrins. The latter hypothesis appears to fit the facts.

Third generation syphilis. Review of the literature and report of a case. James A. Brussel. Arch. Dermat. & Syph., Chicago. July 1939, 40: 70.

Statistics are meager on congenital syphilis extending beyond the second generation. In 1904 Fournier reported the virulent form; other cases have since been reported making a total of 15 in the literature. There must be more frequent occurrences if Whipple and Dunham's estimation is correct that over 11 percent of the 683,000 persons with syphilis who are constantly under observation in the United States have an infection transmitted by the parent. The pathetic part of congenital syphilis is that it is usually discovered "backward;" that is, a child brought to a physician for some minor ailment furnishes the first clue. Such a condition is true for the case here reported.

A child, a girl 8 years old, was brought to her family physician because of swollen glands. Physical examination revealed cervical adenopathy, perforation of the soft palate, and interstitial keratitis. Emotionally she was unruly and regarded as a "problem child" at school. The Wassermann reaction of the blood was positive; the spinal fluid was entirely normal. Her sister refused serologic examination, but her brother pre-

sented no clinical signs of syphilis and his serologic reaction was negative. The father had had Wassermann tests regularly in connection with his work and all were negative. The child's mother was without doubt congenitally syphilitic, but, while her 3 sisters and brother were all serologically positive, acquired syphilis could not be ruled out. One sister was under treatment for dementia paralytica, the brother was hospitalized because of mental illness, and the other sister had been deaf since infancy and had been hospitalized because of a manic-depressive psychosis. The grandmother was dead but it was stated that she had died "from a clot in the brain from blood disease," and the grandfather at 78 years was apparently in good health although he had a positive Wassermann reaction of the blood.

Brussel feels that, measuring this case by the yardsticks of Higoumenakis and of Whipple and Dunham, the offspring of the third generation here described is a victim of third generation syphilis.

Case of tertiary syphilis of the maxillary sinus. Felipe Cora Eliseht and Abel Agüero. *Rev. Asoc. méd. argent.*, Buenos Aires. Apr. 30, 1939, 53: 290.

A case is described in a child 9 years of age who came for treatment for stubborn coryza with copious mucopurulent secretion and intermittent epistaxis. There was nasal obstruction and mouth breathing. Roentgenograms showed marked opacity of the right maxillary sinus and also of the ethmoid cells and frontal sinus of the same side. Examination of a biopsy specimen showed an inflammatory growth, not a malignant tumor. The patient was given anti-syphilitic treatment and improved rapidly. This was a case of gumma from congenital syphilis. The danger in such cases lies in confusion of the gumma with malignant tumor.

Dissecting aneurysms. M. D. Hargrove. New Orleans M. and S. J. June 1939, 91: 678.

Six cases of dissecting aneurysms with autopsy findings are reported. Syphilis as a complication was present in one case and syphilis and arteriosclerosis were both present in the aorta in three cases. The majority of dissecting aneurysms occur between the ages of 40 and 70 years, although one of these patients a syphilitic, was 28 years old.

Syphilis apparently plays a minor role in dissecting aneurysms. The changes caused by syphilis readily produce saccular aneurysms but not dissecting aneurysms. The idea has been advanced, the author says, that there is specific mesarteritis in vascular syphilis which makes splitting almost impossible. Syphilitic aneurysms rarely cause sudden symptoms and are not necessarily associated with hypertension.

Fixed eruption and stomatitis due to sulfanilamide. Adolph B. Loveman and Frank A. Simon. *Arch. Dermat. & Syph.*, Chicago. July 1939, 40: 29.

The authors believe this reported case has several unusual features. The patient, a man 34 years old, was first seen on Oct. 31, 1938 because of a cutaneous eruption accompanied by soreness of the mouth. On Sept. 14 he had been given sulfanilamide for gonorrheal urethritis and he had taken 300 grains (19.2 gm.) during a period of 10 days although the discharge had ceased at the end of 5 days. Four days after he stopped taking the tablets, slightly elevated cutaneous lesions appeared on the back of the neck and in the palm of the left hand and his mouth was sore. These lesions disappeared after 6 or 7 days. About Oct. 2 the urethral discharge again appeared and the man purchased sulfanilamide tablets and took a total of 7 gm. On the third day he noticed a recurrence of

the "spots" in the same areas as before, accompanied by a severely sore mouth. He then reported at the clinic.

After all signs of the stomatitis and dermatitis had disappeared, the patient was given 3 5-grain tablets of sulfanilamide by mouth along with 1 gm. of sodium bicarbonate. The next day there was a flare-up of all previously involved areas and a definite stomatitis. Since Neoprontosil is claimed to be less toxic than sulfanilamide, the patient was given 5-grain tablets of this drug 10 days later. This was followed by another flare-up of the lesions but in a less marked degree, and only a few erosive lesions were seen in the mouth. It was of interest that while a reaction could be elicited with both sulfanilamide and Neoprontosil, the degree of local involvement was directly proportional to the dose administered. Patch tests were done with a 1 percent aqueous solution of sulfanilamide on both normal and previously involved areas. There was a definite although mild reaction on the involved areas only.

Unusual course of lymphogranuloma inguinale with destruction of the hip joint. J. Herzberg. *Dermat. Wehnschr.*, Berlin. June 17, 1939, 108: 673.

The case of a soldier is reported who was infected with lymphogranuloma inguinale by a woman with a rectal stricture caused by lymphogranuloma inguinale. Pain and enlargement of the right inguinal lymph nodes were not noticed until about 1½ years after the first sexual contact with this woman. The Frei reaction became positive 3 weeks after the onset of symptoms. The patient continued to have a septic temperature in spite of incision of the inguinal lymph nodes. He was therefore operated on and marked involvement of the right iliac lymph nodes was found to be present. For this reason he was treated conservatively. He was discharged from the hospital 7 months after admission and at this time had slight weakness of the musculature of the right

leg. Four weeks later he had to be readmitted because of the sudden development of arthritis of the right hip joint. Large amounts of pus were drained from the affected hip. Frei antigen was prepared from this pus which gave strongly positive reactions in patients with lymphogranuloma inguinale. There was no clinical, roentgenologic, or serologic evidence of tuberculosis, syphilis, gonorrhea, or actinomycosis. Osteomyelitis could not be definitely excluded, although the positive Frei reaction would tend to exclude it. Besides drainage of the hip joint, the patient was given 1 tablet of Neoprontosil album 4 times a day until he had received a total dosage of 85 gm. He was much improved by this treatment. The hip joint healed with ankylosis and shortening of the leg. An effusion of the right elbow joint occurred shortly after the involvement of the right hip. This was thought to have been a toxic manifestation.

Fatal hemorrhagic shock following neoarsphenamine. Report of a case. Irving J. Wolman and P. F. Elfeld. *Delaware State M. J.*, Wilmington. May 1939, 11: 84.

A 44-year-old Negro woman was admitted to the Delaware State Hospital in November 1937 for treatment of involutional melancholia of 7 years' duration. Her blood Wassermann reaction was positive, but the spinal fluid was negative. Antisyphilitic therapy was promptly started, and she received 15 weekly injections of 0.6 gm. of neoarsphenamine. These were followed by 12 weekly injections of 2 cc. of iodobismutol, and a third series was started July 22, 1938. The first 2 treatments produced no adverse effects. On August 12 an injection of neoarsphenamine was given and one hour later the patient's gums were bleeding profusely. All efforts to check the hemorrhage were unavailing and she went into a state of shock and died 6 hours later. Necropsy revealed hemorrhagic edema of the lungs and petechial hemorrhages in all parts of the body with hemorrhage into

the gastro-intestinal tract. Other patients who had received injections from the same solution remained free from reactions. This fatality must be attributed, therefore, to some acquired constitutional sensitivity. She had never shown any evidence of anaphylactic sensitivity to neoarsphenamine after previous injections.

Gumma of the orbit. Max Fine. *Am. J. Ophth.*, St. Louis. June 1939, 22: 595.

Of all the conditions in which the ophthalmologist must make a differential diagnosis the most difficult is that of unilateral exophthalmos. One of the conditions producing such exophthalmos, which because of its rarity is unfortunately often not considered until late, is gumma of the orbit. A rule was stated by Meller 25 years ago that in any case of suspected orbital tumor in which the diagnosis is not apparent, a therapeutic trial of antisyphilitic therapy is indicated regardless of the Wassermann reaction, and the advances in syphilology and ophthalmology have made it no less applicable today.

The author, reviewing available literature of the past 25 years, found 24 reported cases in which the diagnosis of orbital syphilis was established. These cases are presented in tabular form. Two cases of gumma of the orbit reported here are the only two on record in the Stanford Clinic since 1913, and during this period approximately 40,000 patients were seen in the eye department and 271,000 in all departments.

Case 1 was a Negro woman, 37 years of age, who complained of pain and impairment of vision in the left eye of 2 weeks' duration. Seven years before she had had an ischio-rectal abscess associated with extensive rectal strictures. The blood Wassermann test had been positive. She had antisyphilitic treatment for a year. A blood Wassermann test was again positive 4 months before admission but she did not have additional treatment. She was given injections of iodobismutol twice weekly and potassium iodide 40 grains daily, and in 10 weeks there was great improve-

ment in the eye. A course of neoarsphenamine was then begun.

Case 2 was also a Negro woman who complained of a swelling over the right eye and severe headache for 2 weeks. The blood Wassermann test was positive, but the patient denied any syphilitic infection. A diagnosis of gummatous periostitis of the supraorbital ridge and gumma of the nasal septum with perforation was made. Antisyphilitic treatment with sobisminol was begun and within 10 days there was definite decrease in the size of the tumor. At the end of 2 months' treatment there appeared to be no difference between the right and left orbits.

The significance of asymptomatic neurosyphilis. Paul A. O'Leary. *New York State J. Med.*, New York. July 1939, 39: 1303.

Asymptomatic neurosyphilis is the manifestation of syphilis which is characterized by a positive spinal fluid test and in which there are neither signs nor symptoms of invasion or involvement of the central nervous system. It may be encountered in any phase of syphilis. O'Leary discusses its significance as lying in these facts: (1) It is the forerunner of clinical neurosyphilis; (2) it responds comparatively well to treatment, and in those cases in which treatment is satisfactory the development of clinical neurosyphilis is prevented; (3) the results of repeated examinations of the spinal fluid can be used as fairly accurate indicators of the response the patient is making to treatment; (4) the results of repeated examinations of the spinal fluid also denote the "trend" of the disease in the central nervous system; in other words they reveal the tendency for the fluid to change to the mild or to the severe (paretic) type; (5) in no other type of neurosyphilis is it possible to appraise as readily the results of the different systems of treatment; (6) the effect of the various schemes of treatment gives an excellent clue to the status of the patient's mechanism of defense against the disease.

Livedo racemosa following "solusalvarsan." G. Brillinger. *Dermat. Wchnschr.*, Berlin. May 20, 1939, 108: 568.

Two cases of livedo racemosa occurring in siblings following exanthemata produced by solusalvarsan are described. The first case was a boy 6 years of age with congenital syphilis. The day after he was given his third solusalvarsan injection a generalized, scarlatiniform, maculopapular eruption of the skin developed. The eruption disappeared after a few days but a blue-violet network (livedo racemosa) of the skin of the trunk and upper and lower extremities remained. An attempt to continue arsphenamine therapy with sodium salvarsan 30 days later was followed by a similar skin eruption followed by an accentuation of the condition of livedo racemosa. A 7 year old brother of the patient also had congenital syphilis. Livedo racemosa developed after he had been given his seventh injection of solusalvarsan. The author assumes that in these siblings a familial liability of the peripheral blood vessels was the probable underlying factor.

On the significance of syphilis in carcinoma of the female genital tract. E. Schrader. *Zentralbl. f. Gynäk.*, Berlin. Apr. 29, 1939, 63 : 930.

A group of 45 women with carcinoma of the cervix and 2 women with carcinoma of the vagina were studied. These women also had latent syphilis. It was demonstrated that these women did not tolerate combined radium and X-ray therapy as well as nonsyphilitic women. This was evidenced not only by greater sensitivity of the skin but also by the occurrence of tenosynovitis of the bladder and rectum. Irreparable anemias and decreased general well-being were relatively frequent. Local tissue damage, such as the production of fistulas, was not observed. Recurrences and the formation of metastases were frequent. There seemed to be no relationship between these manifestations and the type of carcinoma.

DIAGNOSIS

Diagnosis of congenital syphilis. Pathognomonic criteria. William C. Black. *J. Pediat.*, St. Louis. June 1939, 14: 761.

Since no comprehensive code for the diagnosis of congenital syphilis has as yet been established, the author is reviewing and evaluating the existing means of diagnosis in an attempt to formulate an outline of pathognomonic criteria. More refined and judicious use of diagnostic methods is necessary, since the antepartum treatment of infected women has become nearly universal, in order to identify the occasional mildly infected infant among the many babies without syphilis who have been born to treated syphilitic mothers. One of the important axioms of the proper management of syphilis is that the diagnosis must be established before treatment is instituted. It is necessary that a sharp distinction be drawn between a positive and a presumptive diagnosis of congenital syphilis. Occasionally it will not be possible to make a positive diagnosis for a period of 6 weeks to 2 months after birth, but there is no evidence that this delay is harmful. There may be occasional instances in infancy in which treatment would be justified without the support of an absolutely positive diagnosis. Should such a situation arise, consultation with the best available authority in roentgenology, pediatrics, and serology should be obtained.

Criteria accepted as diagnostic of congenital syphilis vary widely in different communities. Pathognomonic evidence of the presence of syphilis in living infants and children is seldom afforded by the results of physical examination but it is to be found in the results of properly interpreted dark-field, serologic, and roentgenologic examinations. The author gives 3 tables to be used as a tentative pathognomonic code in the diagnosis of

congenital syphilis. Table I covers the procedure for the diagnosis of congenital syphilis in young infants, and lists the following procedures: (1) Routine Wassermann tests of all pregnant women, and suitable treatment of every pregnant woman who has or has had syphilis; (2) dark-field examination of umbilical vein scrapings in cases in which there has been inadequate or irregular treatment; (3) cord or peripheral infant blood Wassermann test in every case and titrations in all positive cases; (4) roentgenograms of the long bones within 2 weeks after birth in those cases in which the presence of syphilis is fairly probable; (5) repeated infant blood Wassermann tests at 2-week intervals with titration in cases in which the original test was positive; (6) repeated roentgenograms of the infant at one month or 6 weeks of age when the diagnosis is still in doubt; (7) repeated dark-field examinations of any suspicious lesions; (8) spinal fluid examinations of infants in whom the presence of syphilis is fairly probable when subsequent examinations have not revealed positive diagnostic results.

Table II—Tentative criteria for positive diagnosis of congenital syphilis: Diagnosis established by dark-field examination, by serologic tests, and by roentgenologic osseous examination. Table III—Tentative criteria for establishing the absence of congenital syphilis in untreated infants and children: (1) At birth, nonsyphilitic mother; (2) at 4 months, 2 negative blood tests and 1 negative spinal fluid serologic reaction; (3) after 2 years, 2 negative blood tests and 1 negative spinal fluid serologic reaction.

The value of examination for gonococci during the menstrual period. F. Schmidt-La Baume and W. Lehmann. *Dermat. Wchnschr.*, Berlin. May 27, 1939, 108: 581.

During the period from June 1937 to December 1938 a total of 328 smears obtained during the menstrual period were examined. Of these 35 (10.67 percent) were positive for gonococci. Most of the

positive smears (21) were obtained on the first day of menstruation. In 8 percent of the patients from whom the material was obtained it was not a first infection. If smears had not been made during the menstrual period, 60 percent of the cases could not have been diagnosed. In the other 40 percent, gonococci were repeatedly found. Among prostitutes, 40 percent had reinfection (80 percent diagnosed during the menstrual period). The authors point out the value of examinations during the menstrual period especially in prostitutes because of the high incidence of chronic infection in them.

Systemic manifestations of lymphogranuloma venereum. With illustrative case reports. Alexander B. Gutman. *New York State J. Med.*, Albany. July 15, 1939, 39: 1420.

Lymphogranuloma venereum is not considered a disease entity. Apart from the constitutional reactions attending the acute phase, the systemic effects of this disease have received little recognition and, after an analysis of 135 French positive cases from the Presbyterian Hospital, Gutman believes these aspects deserve more general medical interest.

He finds that ordinarily the constitutional reactions to the infection in the acute initial phase offer no serious diagnostic problem since buboes or localizing genito-urinary or rectal signs reveal the nature of the underlying infection. Patients who present marked and prolonged hyperpyrexia without these localizing signs may simulate typhoid or undulant fever, sepsis, appendicitis, etc., which doubtless contribute to the total of patients with "fever of unknown origin." In his discussion of the constitutional reactions in the late and chronic stages of the disease, the author says that the resulting clinical picture is extremely varied. Often the chronic course is dominated by prolonged fever and general constitutional reactions accompanying protracted suppuration and fistulization of regional lymph nodes. The most significant complications are those affecting the intestinal tract. Var

is forms of ulcerating and proliferating proctitis without stricture are common as well as extensive involvement of the sigmoid flexure. There were 3 cases of those reviewed in which necropsy indicated death from peritonitis following intestinal perforation.

The possible mechanisms which may cause the systemic manifestations of lymphogranuloma venereum are discussed under (1) acute "toxic" constitutional reactions which Gutman believes are due to early dissemination of the virus, (2) systemic manifestations due to the allergic state, (3) those due to hyperglobulinemia, and (4) those directly attributable to extension or dissemination of the virus. Special, interesting cases illustrating each phase are discussed at length.

Gutman says that more necropsy reports and animal transmission experiments with human organ extracts are needed in order to determine how many of the systemic manifestations of lymphogranuloma venereum can be attributed to generalized dissemination of the virus. That such systemic manifestations occur, however, and with sufficient frequency to be of general medical interest, appears to be well established.

In the discussion, Dawson calls attention to a subacute form of arthritis which he has encountered in 16 patients whose Frei tests were positive. Curth says more than 200 cases of lymphogranuloma venereum have been seen at the Vanderbilt Clinic since 1931. There were 10 cases with syphilitic chancres followed by typical lymphogranuloma venereum adenitis, and several cases of mixed infections of lymphogranuloma venereum with chancroid or venereal granuloma. Kornblith says that in a group of 375 cases observed at Mt. Sinai Hospital, arthralgias developed in 10 cases, hepatosplenomegaly was present in 6 cases, generalized adenopathy simulating infectious mononucleosis or lymphatic tuberculosis was present in 5 cases, and a maculo-erythematous rash occurred in 3 cases.

On the skin test in lymphogranuloma inguinale. II. Wilhelm Frei. J. Invest. Dermat., Baltimore. June 1939, 2: 119.

In a previous paper Frei stated that the most common errors in the use of the lymphogranuloma inguinale skin test result from the contamination of the vaccine with living or dead bacteria. The danger of contamination of this particular vaccine is especially great since it is prepared without an antiseptic and thus furnishes an excellent culture medium. In this connection attention is called to the fact that in some localities in this country the lymphogranuloma inguinale vaccine is preserved in vials equipped with perforable rubber stoppers and fitted for repeated use, instead of in small ampules each containing material for one test only. A preliminary experiment was reported in which these rubber caps, disinfected with 80 percent denatured alcohol, were used for sealing the vials.

Experiments using rubber stoppers with depressed centers for sealing and a tincture of iodine for the disinfectant are reported in this paper as giving much better results. Only 2 contaminations occurred in the filling of 89 vials and only one contamination in the using of 87 vials. Whether the difference between the results of the earlier and the later experiments is due to an improvement in technic of sterilization or to superiority of the depressed rubber stoppers over the rubber caps is not discussed. It is questionable whether the precautions of strictest sterility and permanent refrigeration in the use of vials can always be carried out in practice. For this reason Frei believes it is preferable to continue putting up the lymphogranuloma inguinale vaccine in small ampules. He says that since the preparation of the vaccine and the performance of the test are responsible tasks, it is preferable that both procedures be centralized at selected institutions.

Clinical evaluation of serologic reports.

George W. Binkley. Ohio State M. J., Columbus. July 1939, 35: 721.

Factors influencing the results and interpretation of serologic tests are (1) fallibilities inherent in the technic—paradoxical results, questions of specificity and sensitivity, and lack of precision of qualitative reports; (2) factors characteristic of the course of the disease affecting serologic results and subject to variation in different persons—syphilitic reaginemia in the newborn and seronegativity during the course of the disease; (3) the effect of chemotherapy on the demonstration of reagins in the blood, subject to individual variations.

Under technical considerations the author discusses the types of tests used, sensitivity of tests, exclusion tests, variations in flocculation tests, technical variations, significance of the titer of reagins, qualitative reports, quantitative reports, specificity of tests, and the confusion resulting when the patient has certain other diseases (yaws, rat-bite fever, relapsing fever, malaria, or infectious mononucleosis).

Diagnosis may be made with irrefutable evidence from the history, clinical findings, and serologic study. A patient with a positive serologic test but without definite clinical symptoms should not be diagnosed as having the disease until a confirmatory test is made. If a strongly positive reaction is reported a second time it is fair to assume that it is due to syphilis reagins, provided other possible causes of false positive results have been ruled out. The spinal fluid should be examined before chemotherapy is started in cases of late syphilis. In 1939, the syphilologist treats syphilis by schedule, because the serologic test has proved to be an unreliable guide to therapy.

The Laughlen test in the diagnosis of syphilis. Walter F. Lever and William K. Massie. Arch. Dermat. & Syph., Chicago. July 1939, 40: 45.

The Hinton test is used routinely at the Massachusetts General Hospital on all specimens of serum sent to the lab-

oratory. The standard Wassermann test is performed on the serums giving a positive Hinton reaction, and the Kahn test is done in emergencies. The need for a more rapid and more easily performed test than is now available led to a comparative study of the Laughlen test with the tests in use.

A series of 2,220 Laughlen tests were compared with the Hinton and the Wassermann; and a series of 780 with the Hinton, the rapid Hinton, the Wassermann, and the Kahn test. In the first group, 442 serums were presumptively syphilitic and of this group the Hinton reaction was positive in 431 (97.5 percent), the Laughlen in 334 (75.6 percent) and the Wassermann in 189 (42.7 percent). The number of false positive Laughlen reactions in the series of 1,770 normal specimens was 13, or 0.7 percent. The second series of 780 was for a further check. In 390 presumptive syphilitic specimens the Hinton reaction was positive in 383 (98.2 percent), the rapid Hinton in 371 (95.1 percent), the Laughlen in 300 (76.9 percent), the Kahn in 268 (68.7 percent), and the Wassermann in 177 (45.4 percent). Among the 390 normal specimens there were 3 with a positive Laughlen reaction (0.8 percent) and 8 with a positive rapid Hinton (2.1 percent); the Kahn revealed no false positive results. Therefore the Laughlen test gave 16 false positive results among 2,168 normal specimens, or an average specificity of 99.3 percent, and 634 positive results among 832 presumptively syphilitic specimens, or an average sensitivity of 76.2 percent.

The authors feel that the Laughlen test deserves more attention than it has been given by serologists and syphilologists. It has been found to be easy and fast (15 to 20 minutes to perform) and the reading is relatively easy for those who have had experience with it. The sensitivity and specificity of the test warrant its use as an emergency test in preference to any other test performed on this series. It was found to be less sensitive but more specific than the rapid Hinton and less specific but more sensitive than the Kahn test.

the significance of serum protein and bone marrow changes in lymphogranuloma inguinale. O. Gsell. Klin. Wchnschr., Berlin. June 3, 1939, 18: 778.

The case of a 64-year-old woman with lymphogranuloma inguinale is reported. She gave a history of having had too frequent defecation with an associated discharge of blood and pus from the rectum 6 years ago. A diagnosis of ulceromorrhagic proctitis and hemorrhoids was made at that time. The blood Wassermann reaction was negative. A biopsy was refused by the patient. She continued to have the same symptoms.

In 1938 she was admitted to the hospital because of diarrhea. At this time she was found to have a relaxed anal sphincter with many polypoid growths and nodular infiltrates of the anus and vulva. There was no palpable stenosis of the rectum. Histologic examination of tissue removed through the rectoscope revealed granulation tissue with infiltrates of leukocytes, plasma cells, and eosinophils. The blood Wassermann, Sachsberg, and citochol reactions were negative. A diagnosis of genito-anorectal lymphogranuloma inguinale was made. The patient had a moderate secondary anemia, a marked increase in the sedimentation rate of the red blood corpuscles (141 mm. after 1 hour), increased serum viscosity (2.75), marked hyperproteinemia (10.9 mg. percent according to the method of Kjeldahl), as well as hyperglobulinemia (6.6 mg. percent according to the method of Butler and Montgomery). The albumin-globulin ratio was 10:90 as determined by the method of Naegeli-Rohrer. The Takata reaction according to Jezler was strongly positive. The myelogram obtained from histologic examination of material obtained by sternal puncture showed increased leukopoiesis and a considerable decrease in reticulum cells, especially plasma cells. The author points out that generalized lymphogranuloma inguinale is an inflammatory disease of the reticulo-endothelial system.

Gonococcus cultures as an aid to diagnosis. L. H. Winer and A. Leibovitz. Journal-Lancet, Minneapolis. June 1939, 59: 267.

In acute cases of gonorrhea the authors have found that the smears were positive as frequently as the cultural growths, but in the chronic cases the cultural was found to be superior to the smear method. In 24 positive chronic cases examined in the past 3 months only 14 were found to be positive by the smear method whereas 23 were positive by the cultural method. These patients with negative smears would ordinarily have been classified as having nonspecific urethritis and would have been epidemiologically dangerous as carriers. All patients before being discharged as cured should have negative cultures of the prostatic fluid and urethral mucus.

The value of repeated cardiovascular examinations of patients under treatment for syphilis. H. Arenberg, S. J. Leland and J. J. O'Connor. Hosp. News, U. S. Public Health Service, Washington. June 1, 1939, 6: 23. (Mimeographed.)

Since syphilis is known as one of the important etiologic factors of heart disease, the authors feel that all syphilitic individuals should be considered as potential cardiac patients. The literature reveals that there is a great discrepancy between the number of cases in which there was a clinical diagnosis of cardiovascular disease and those in which there were post-mortem findings; in one report only 4 percent of the 105 cases in which syphilitic aortitis was proved at necropsy had been diagnosed clinically during life. The authors feel that syphilitic aortitis can be diagnosed much earlier than is usually done if routine examination and reexamination of all syphilitics in a heart clinic are done throughout the course of treatment. A study of such a course was made by the authors in a hospital during the past year. In addition to the usual history and examination, a fluoroscopic exami-

nation and a roentgenogram of the heart was made for each patient. Two hundred patients ranging in age from 19 to 51 years are included in this preliminary report. There were 84 in the group classified as "early," whose initial lesions were known to have occurred less than 4 years prior to the study; 93 in the "late" group, containing those whose initial lesions occurred more than 4 years previously, and 23 were designated as "unknown."

Among the 200 cases studied, there were 24 cases of asymptomatic cardiovascular disease attributable to syphilis. Three of these 24 cases were in the early group. Of the 21 in the late and unknown groups, 9 had had no treatment or less than 2 courses. Nine percent were found to have uncomplicated aortitis; 1.5 percent were complicated by aortic insufficiency and aneurysm and 1.5 percent showed electrocardiographic evidence of coronary involvement. This is a considerably smaller incidence of aortitis than has been found by many investigators, but this group was composed entirely of seamen and over 40 percent were in the early group.

The authors urge periodic examination of all syphilitics under treatment in heart clinics of U. S. Public Health Service Hospitals throughout their course of treatment, and they state that the findings should be incorporated in the treatment records making it possible to conduct additional and more extensive studies.

TREATMENT

Treatment-resistant syphilis. An evaluation of the causative factors in 18 cases. Walter Beckh and George V. Kulchar. *Arch. Dermat. & Syph.*, Chicago. July 1939, 40: 1.

Reports in German and French literature give the impression that resistance to treatment is being observed with in-

creasing frequency, but American reports have dealt with small numbers of cases. The authors are reporting on 18 instances of treatment-resistance which they have encountered during the past 6 years in patients with early syphilis. The criteria for the diagnosis was (1) persistence of the initial lesions despite adequate therapy, or recurrences appearing during treatment, and (2) persistence of *Spirochaeta pallida* in the lesions despite adequate treatment. In all patients the treatment-resistance occurred during therapy.

The clinical manifestations of treatment-resistance were variable and for the most part involved the skin and mucous membranes. Three of the patients were refractory to treatment from the beginning; in 2 the initial lesions were resistant but eventually involuted only to be followed by refractory recurrences, and in 13 the original lesions responded normally but clinical manifestations of resistance appeared subsequently. Continuance of the treatment used before the clinical appearance of the refractory state proved successful in only 1 of the 7 cases in which this measure was tried; however, a change of drug was effective in 10 out of 13 cases. Intensification of treatment, either through increase in frequency of administration or by a combination of drugs was effective in 4 of 7 cases. Fewer than 10 percent of the patients receiving therapy was successful in 2 of 4 cases.

Little evidence could be found that specific host factors are primarily concerned in the production of treatment-resistance. Likewise, treatment-refractoriness could not be ascribed to infection with a treatment-resistant strain of *Spirochaeta pallida*.

Treatment-resistance was observed to occur with much greater frequency in patients treated by the "combined" system of therapy than in patients receiving the "alternating" type of treatment. It is suggested that the high incidence of treatment-resistance observed among patients receiving the "combined" type of therapy is due to prolonged undosage with the arsphenamines.

nical results of fever therapy. Earl J. Elkins and Frank H. Krusen. Arch. Phys. Therap., Chicago. June 1939, 20: 346.

Gonorrhea has held the most important place in the use of fever therapy in the authors' department at the Mayo Clinic. They have analysed the results of the treatment of 415 patients who have had a definite diagnosis of gonorrhea, positive cultures and satisfactory amount of treatment. In 94.1 percent of this group, 1 to 5 negative cultures were obtained from the urethra or cervix after treatment.

From 1933 to 1936 an average of 5.4 treatments of 6 hours with body temperature of 106.7° F. (41.5° C.) were given. In 1937 a new routine was started, 10-hour sessions being used. Of 43 cases in which positive cultures were obtained before treatment, in 93 (93.3 percent) cultures were negative after treatment. Local heating of the pelvis is now used routinely in all cases of gonorrheal infection of women. The Herman-Horowitz vaginal applicator and an electrode with conventional diathermy is used. This pelvic heat is applied after 5 or 6 hours of body temperature of 106.7° F., after which the body temperature is reduced to 103° to 104° (39.3° to 40° C.) and the pelvic and rectal temperatures are maintained between 107° and 110° F. (41.7° and 43.3° C.) for the remainder of the 10-hour session. Oral and axillary temperatures are recorded as controls. Any sudden elevation of the temperature, pulse rate, blood pressure, or early indication of coma is considered as a danger sign.

The criteria for determining the probability of clinical cure before dismissal of patients were definite clinical improvement and at least 4 negative cultures for *Neisseria gonorrhoeae*, with one post-menstrual culture in women. Replies from questionnaires sent to 198 patients showed that recurrences were experienced in probably not more than 5 or less than 3 percent of the cases.

Since the introduction of sulfanilamide, artificial fever has been used less

often. There is a certain percentage of failures from sulfanilamide treatment, however, and in those cases the advisability of fever therapy was considered when there was no improvement after 10 days of sulfanilamide treatment. Since July 1937, 443 cases of gonorrhea have been treated by means of fever therapy and sulfanilamide. The procedure is to administer 80 grains of sulfanilamide daily for 2 days and then fever therapy for 10 hours at a body temperature of 106.7° F. The average number of 10-hour sessions necessary has been 1.2 per patient. Negative cultures were not obtained in 2 (4.6 percent) of the 43 patients. The patients who have been given the combined chemotherapy apparently had extremely resistant gonorrheal infections.

In the series of 84 patients treated by 10-hour sessions, negative cultures resulted in 95.2 percent, and the average number of treatments required was 1.1. In 76 percent of the cases negative cultures were obtained after a single session.

Sulfanilamide and gonorrhea—present status. Oscar F. Cox. Bull. Genito-infectious Dis., Boston. May 1939, 3: 3.

The fact that a period of latency may follow an active gonococcal infection has been ignored by many who have reported sulfanilamide cures. That sulfanilamide has not eliminated the possibility of latency is shown by the experience of workers at the Boston dispensary who demonstrated the presence of gonococci in some patients 4 months after provocative tests had failed to reveal either pus or gonococci in stained smears of the prostatic secretion. A negative smear 2 or 3 weeks after the disappearance of the discharge is not evidence of cure; to report it as such is misleading and may cause great harm.

The mode of action of sulfanilamide on the gonococcus is not yet known. Some of the best work reported has shown that the drug enhances the bacteriostatic properties of the blood, urine,

spinal fluid, and synovial fluid. Other studies suggest a neutralizing effect on gonotoxin. It has not been demonstrated yet that sulfanilamide is bactericidal to the gonococcus when it is present in man.

It has been suggested by some that the drug retards the production of antibodies and therefore should not be prescribed during the first few weeks of the disease. Keefer and Rantz, however, have shown that the sulfanilamide does not interfere with the formation of the antibodies utilized in the complement fixation test. In the author's experience, 73 percent of patients responded well to treatment when the drug was given at the first visit. If the drug is given early it will usually prevent extension of the disease. There seems to be no justification at present for withholding this therapeutic agent after the diagnosis has been made.

The author states that 60 grains per day at first has resulted in as many satisfactory clinical responses as an initial dosage of 80 grains per day. The larger dosage causes many more undesirable side-effects such as weakness and marked dizziness (dangerous for automobile drivers). Most clinicians have observed their best results when local treatment has been combined with sulfanilamide. If a clinical response is noted within the first few days the drug should probably be continued for 2 or 3 weeks, but if such a response is not observed within 5 days it is wise to discontinue its use and try it again after an interval of 10 to 14 days. A satisfactory clinical response does not result from increasing the dosage in sulfanilamide failures.

Alvea, Daniel and Yates have shown that the blood concentration of sulfanilamide is the same in individuals who are given 500 cc. of fluid per hour as in those given only 30 cc. of fluid per hour. The total amount of the drug in the urine is not affected by the fluid intake.

Sulfanilamide does not sterilize a walled-off, non-draining focus. This fact may explain why local treatment seems to add to the efficacy of the drug.

Sulfanilamide and some of its allied drugs have been valuable in the treatment of gonorrhea, although their limitations must be well understood. Clinical response to treatment does not mean absence of communicability. Culture studies probably constitute the most effective method for detecting the gonococcus in latent cases.

Experience in the chemotherapy of gonorrhea. K. Goyert. *Dermat. Wehnschr.* Berlin. May 20, 1939, 108: 561.

The various treatment methods applied to a group of 300 patients (147 males, 153 females) who were treated with sulfanilamides from Oct. 1937 to Feb. 1939 are discussed. It was found that general women responded better to treatment with sulfanilamides than men. The results could be somewhat improved in men by giving vitamin C. Acute gonorrhea of the male was treated locally with silver preparations prior to the administration of sulfanilamides. This method was later discontinued in favor of vaccine treatment during the first days of the infection. The women were given all chronic cases in which sulfanilamide were given at once. No severe by-effects were observed with either uliron or disseptal C. By-effects occurred less frequently with courses of treatment than with the continuous method. Twenty patients were observed by the author a period of 14 days after the conclusion of treatment. Daily microscopic examinations and two Neumann cultures were made during this period.

Studies on the absorption and action of disseptal C. J. Hämel and T. Lisch. *Dermat. Wehnschr.*, Berlin. May 1939, 108: 537.

The complement fixation reaction in gonorrhea was carried out on all patients treated for gonorrhea by the author. The antigen was obtained from Labopharma Co., Berlin. Of the patients who were successfully treated with disseptal C about two-thirds had a negative complement fixation reaction before they had received treatment. The other

bird had a positive reaction. Among the patients who had recurrences after the course a negative complement fixation reaction occurred as frequently as the positive one. The authors conclude from this experience that the complement fixation reaction has no prognostic significance. They agree with Mulzer who is of the opinion that the reaction of gonococci to media containing disseptal C furnishes no indication as to whether the patient from whom the gonococci were obtained will respond to septic treatment or not.

A group of patients consisting of 46 men, 58 women and 3 children was treated with disseptal C. Acute gonorrhea in the male was first treated with gonococcus vaccine (compligon) or 40 percent olobintin. All chronic cases received no preliminary treatment. The men used potassium permanganate irrigations whereas no local treatment was given to the women or children. The drug was administered in 3-day courses separated by rest periods of 4 to 6 days. During the course 6 tablets of 0.25 gm. disseptal C each were given during each day. As a rule 2 courses of treatment sufficed. In those cases in which 3 courses failed to bring about a cure the total dosage was increased to 6.75 gm. for the next course. The largest total dosage given was 27 gm. Of 24 men with acute gonorrhea 8 had recurrences after an apparent cure, but all of them were finally cured. Of 22 men with chronic gonorrhea all except 3 were finally cured. One course was sufficient to bring about a cure in 33 of the male patients. Of the 58 women 48 were cured with 1 course, 6 more were cured with further treatment, and in 4 gonococci persisted. These 4 were finally cured with local therapy. Of the 3 children with gonorrheal vaginitis, 2 were cured after 1 and the other after several courses.

Following treatment the men received 3 and the women 4 provocative tests. Culture controls were also made regularly on Neumann's media. At least one provocative test was made in women after the menstrual period.

In order to demonstrate the relationship between resorption of the drug and therapeutic effect, the blood serum level of disseptal C was determined in these patients on the first and last day of each course of treatment. This serum level was found to vary between 1.0 and 2.5 mg. percent. In most patients the level was higher during the second and third courses than during the first course. There were also great individual variations in the serum level. No relationship was found to exist between gastric acidity and absorption. The administration of hydrochloric acid did not increase absorption. The authors assume that the drug is absorbed from the small intestine. The greater the serum level of the drug the better was the therapeutic effect. No serious byeffects were observed.

Gonorrheal ophthalmia cured after one week's treatment with sulfanilamide.

S. Hanford McKee. Arch. Ophth., Chicago. June 1939, 21:1035.

The author reports the case of a 23-year-old man, with severe gonorrheal ophthalmia and urethritis, who was cured after one week's treatment with sulfanilamide. Treatment included the usual frequent irrigations with a warm solution of boric acid followed by the instillation of drops of a 25 percent solution of mild protein silver. A Buller shield was supplied to the unaffected eye. In addition to the local treatment 15 grains of sulfanilamide was taken with 5 grains of sodium bicarbonate every 6 hours.

On the third day of treatment the discharge was noticeably less, and on the fourth day the infection was improving satisfactorily. On the fifth day the discharge had almost disappeared, and a prolonged search for gonococci in an epithelial smear gave negative results. Two days later the patient was discharged as well.

In previous cases, infections of this kind often entailed the employment of two graduate nurses for 5 to 6 weeks.

Fernandez and Fernandez recently reported on sulfanilamide in the treat-

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TRYPARSAMIDE IN THE TREATMENT OF SYPHILIS

A Review of the Literature

JOSEPHINE HINRICHSEN, M. D.

United States Public Health Service, Washington, D. C.

HISTORY OF THE DRUG: ITS PHARMACOLOGY AND TOXICOLOGY

THE AMIDE of N-phenylglycine-p-arsonic acid was first made and studied by Walter A. Jacobs and Michael Heidelberger of the Rockefeller Foundation in 1915 (62). Soon thereafter biologic studies of this substance, A 63, whose sodium salt was later called "tryparsamide", $C_6H_4(NHCH_2CONH_2) \cdot (AsO : OH : ONa)$, were carried out by Wade H. Brown and Louise Pearce, also of the Rockefeller Foundation (12, 110). They found that different species of animals tolerated large doses of tryparsamide well and that the substance could be administered intraperitoneally, subcutaneously, intramuscularly, and intravenously without untoward effects. Only dosage close to the minimum lethal dose produced toxic effects and the recovery of animals from such dosage was rapid and complete. This low toxicity is remarkable in view of the fact that tryparsamide contains 25.32 percent of arsenic. The lethal dose varies between the extremes of 0.75 and 2.75 gm. per kilogram of body weight for the different species in which it has been tested and for different routes of administration.

There are two different symptom complexes of intoxication—nutritional and nervous. Nutritional disturbances are indicated chiefly by a loss of appetite, weakness, loss of weight and, occasionally, by diarrhea. In moderate doses, tryparsa-

mide produces a remarkable stimulative effect on the animal organism. There is improvement in general appearance, activity and weight. The nervous system symptoms are pronounced tremors with incoordination of movements and in extreme cases clonic spasm usually associated with some weakness or complete prostration. With remission of these early symptoms a tic develops in mice which is characterized by peculiar jerky movements of the head and occasionally by the continuous circling movements of dancing mice. Voegtlin, Smith, Dyer and Thompson (164) in a later study of this sort reported the same motor disturbances in mice which had been injected with large doses of tryparsamide and of oxyamino (3-amino-4-oxyphenylarsonic acid). According to them these motor disturbances were first described by Ehrlich as occurring in mice (dancing mice). Voegtlin and his coworkers considered these symptoms, as well as those involving the optic nerve, to be evidence of penetration of arsenic into the nerve tissue and that the substance produced more or less permanent injury of certain neurons (neurotropism).

These authors also injected suspensions of *Trypanosoma equiperdum* into the cranial subarachnoid space of rabbits. Immediately afterwards (as soon as the animals had recovered from the anesthetic) they were injected intravenously with various arsenicals, including arsphenamine, neoarsphenamine, tryparsa-

amide, oxyamino and sulfarsphenamine. At the end of 24 hours the animals were exsanguinated from the heart, specimens of cerebrospinal fluid were taken from the several subarachnoid spaces, and microscopic examination for trypanosomes was made. Absence of trypanosomes from the cerebrospinal fluid was taken as evidence of the permeability of the meninges for the arsenical under consideration or some trypanocidal derivative thereof. It was found that tryparsamide had the greatest trypanocidal effect but that sulfarsphenamine was almost as effective. The other arsenobenzene derivatives, including arsphenamine and neoarsphenamine, were found to penetrate into the cerebrospinal fluid with considerable difficulty and to exert only a slight effect upon the trypanosomes in the subarachnoid space. The authors concluded, on the basis of these experiments, that sulfarsphenamine, tryparsamide, and oxyamino are substances of superior penetrative power.

Since Voegtlin, Smith, Dyer and Thompson's work "high penetrability for nervous tissue" has been more or less accepted as a definite property of tryparsamide. However, it seems important to differentiate between penetration of the meninges and penetration into the nervous tissue itself; also to differentiate between the direct effect of tryparsamide on trypanosomes and the direct effect on *Spirochaeta pallida*. It is known that tryparsamide will kill trypanosomes *in vitro* and *in vivo* but that, on the contrary, it has little or no effect on the spirochetes contained in the lesions of experimental syphilis or in the primary and secondary lesions of syphilis in man, as was demonstrated in the preliminary clinical work of Pearce and Brown (110, 112) and later by Moore, Robinson and Keidel (95). Dubois (33) describes the case of a man who had been on treatment with tryparsamide for several years because of chronic trypanosomiasis when he developed a chancre. During the incubation period of syphilis he had been given seven weekly injections of 2.5 gm. each of tryparsamide. In other

words, there is not an exact analogy between penetration of nervous tissue with destruction of *Spirochaeta pallida* in this tissue and penetration of the meninges with destruction of trypanosomes contained in the cerebrospinal fluid, or even in the brain and spinal cord.

Raiziss and Severac (116), using the same method that was employed by Voegtlin and coworkers, found arsanilic acid to be the most effective arsenical in destroying trypanosomes which had been injected into the cranial subarachnoid space of rabbits, but tryparsamide, because of its lower toxicity, had the highest chemotherapeutic index, namely 12. It was found that 150 mg. per kilo of tryparsamide was definitely an effective dose. Two experiments were done with spirochetes injected into the cranial subarachnoid space, followed by the intravenous injection of tryparsamide in dosage of 150 to 300 mg. per kilo. One of the rabbits died 6 weeks later without having developed syphilitic lesions. The interval was too short, however, to determine whether the spirochetes had been destroyed. The other rabbit received a dose of 300 mg. per kilo of tryparsamide which did not prevent the generalization of syphilis, with development of scrotal and testicular lesions. No spirochetes could be demonstrated in the spinal fluid although observations were made from a few days after the inoculation until a year later.

Certainly, the evidence for penetrability of tryparsamide into nervous tissue is not entirely clear-cut. Mehrtens, Kolb and Marshall (89), using the Sangre and Black modification of the Gutze method, determined the arsenic content of the spinal fluid after intravenous injection of arsphenamine and tryparsamide preceded in more than half of the cases by meningeal irritation produced by the administration of autoserum. They found only traces of arsenic in the spinal fluid after injection of 0.6 gm. of arsphenamine, even with meningeal irritation. When tryparsamide (3.0 gm) was injected, from a trace to 0.019 mg. of arsenic was found per 10 cc. of spinal

fluid, and after meningeal irritation from 0.0188 to 0.0236 mg. In this connection it is interesting to mention the recent work of Vonkennel and Kimmig (165) with solvarsin (the ethanolamine of 4-hydroxy-3-ethylamino-phenyl-arsonic acid), a pentavalent arsenical used in Germany in the treatment of central nervous system syphilis. They found that under normal conditions of meningeal permeability none of the drug could be found in the spinal fluid (Marsh method). On the other hand, in cases of purulent and epidemic meningitis, one to three intramuscular injections of the drug were followed by the finding of from one to three plus arsenic in the spinal fluid. Fordyce and Myers (45) found experimentally that the brains of rats contained nine times greater arsenic concentration after silver arsphenamine (representing one-fifteenth the amount of arsenic injected), than after tryparsamide. Based upon this work, as well as upon clinical determinations of arsenic concentration of the spinal fluid after the injection of various arsenicals, they concluded that tryparsamide does not possess unusual penetrating power for the nervous system. In 14 percent of their patients no arsenic could be found in the spinal fluid after administration of tryparsamide intravenously. Some years later Cornwall, Bunker and Myers (27) made comparative arsenic determinations of the spinal fluid of five patients with general paresis after intravenous injection of 3.0 gm. of tryparsamide and after intravenous injection of 0.2 gm. of silver arsphenamine. The arsenic content of the fluids after tryparsamide was between 1 and 3 mg. percent, with the exception of the 12-hour interval when it was slightly higher than 5 mg. percent. The amounts of arsenic found after silver arsphenamine were three to eight times more than those recovered after tryparsamide. From this they conclude that the favorable effects reported in neurosyphilis following the use of tryparsamide cannot be ascribed to the quantity of arsenic which enters the spinal fluid.

Tryparsamide is very rapidly removed from the blood stream, according to the studies of Fordyce, Rosen and Myers (44), who found the maximum quantity of arsenic (35.9 mg. percent of dried specimen) in the blood stream immediately after injection. At the end of 15 minutes only 7.65 mg. percent had remained in the blood stream and at the end of 72 hours only 0.012 mg. percent.

In Lorenz's (82) preliminary report on the use of tryparsamide in the treatment of neurosyphilis it was stated that 80 to 90 percent of the drug was eliminated in the urine in the first 24 hours after its administration. After this primary rapid elimination there was a very slow, evenly maintained level for as long as 15 days. The concentration of arsenic in the blood (using 5 gm. doses) was as high as 0.03 mg. per cc. on the second day, on the fourth day rapidly dropping to 0.005 mg. In parallel studies of the spinal fluid and urine as high as 0.02 mg. per cc. of spinal fluid was found 2 hours after the injection. At the same time 2.5 mg. per cc. was found in the urine. A comparable concentration of arsenic in the spinal fluid to that in the blood occurred as early as 3 hours after administration.

Young and Hamilton (172) observed that at least part of the tryparsamide injected was excreted unchanged in the urine.

Young and Muehlberger (174) noted that 88 to 95 percent of tryparsamide was excreted in the urine within the first 24 hours. Traces of arsenic were eliminated in the urine for the next 5 to 7 days in three out of four persons studied. In the fourth, traces of arsenic were found in the urine for a period of 3 weeks.

Osborne, Putnam and Hitchcock (108) made histologic studies for the presence of arsenic trisulfide crystals in the organs of rabbits which had been previously injected with therapeutic and lethal doses of arsphenamine, neoarsphenamine, sulfarsphenamine, and tryparsamide. They observed that there was no evidence of any appreciable storage

of arsphenamine in therapeutic doses. No appreciable amount of arsenic was found in the parenchyma of the central nervous system after the administration of arsphenamine, neoarsphenamine, or sulfarsphenamine. Following the administration of therapeutic and lethal doses of tryparsamide, appreciable quantities of arsenic were found in the parenchyma of the brain and spinal cord. Arsenic was present in both the gray and the white matter, chiefly in the form of small groups of crystals around the smaller blood vessels. After lethal doses of tryparsamide considerable amounts of arsenic were seen in the kidneys and the entire intestinal tract and only very small amounts in the liver.

Tryparsamide was first used therapeutically in the treatment of experimental trypanosome and spirochete infections by Pearce and Brown (110). It was found to possess the therapeutic ratio in mice of one-twelfth to one-eighth the tolerated dose. Well-developed infections in rabbits could be cured with the same unit dose that was capable of curing infections in mice. The spirocheticidal action was observed to be distinctly less than its trypanocidal action. In *Spirochaeta pallida* infections in rabbits large doses of the drug were required to cause a disappearance of spirochetes and the permanent healing of active primary lesions. The therapeutic index was 1:1 or at most 1:2. Tryparsamide was next applied to the treatment of human trypanosomiasis in the Belgian Congo by Pearce (111). She found that the drug had marked trypanocidal activity in human trypanosomiasis caused by *T. gambiense*.

In regard to syphilis there was at first some uncertainty as to what might be accomplished, since its use in this disease had to be based on considerations other than spirocheticidal action. The successful treatment of rabbits, infected with trypanosomes, in which infection the organisms reach the central nervous system, indicated an apparently high degree of penetrability and curative action of

the drug. It had also been observed that tryparsamide had a favorable influence upon the course of experimental syphilis apart from any spirocheticidal action, the drug possessing only slight spirocheticidal power. A preliminary clinical trial in the treatment of syphilis was made by Pearce and Brown (112) in 1919. They treated syphilitic patients with indolent or regressing primary and secondary lesions. Healing of the lesions was promoted and there was some change in blood serologic findings. A few patients with active primary or secondary lesions were treated but it was found that the lesions were either unaffected or their activity increased. The drug was therefore discontinued for the treatment of this stage of syphilitic infection. It was thought that central nervous system syphilis, especially general paresis, presented theoretically favorable conditions for the use of tryparsamide. The first study of the effect of treatment of central nervous system syphilis with tryparsamide was made at the suggestion of Brown and Pearce by Loevenhart and Lorenz of the University of Wisconsin. After the publication of the results of treatment of neurosyphilis by Lorenz, Loevenhart, Bleckwenn and Hodges in 1923, many requests for the drug were made. It was decided, however, to give the drug further clinical trial by a number of clinicians whose experience and facilities made it possible for them to carry out carefully controlled studies. By the middle of the year 1924 it was on trial in 60 clinics and institutions in the United States, 6 in Canada, 5 in Great Britain, 9 in France and 1 in Switzerland. Tryparsamide was placed on the market in January 1925. It has never become popular in Europe with the possible exception of Great Britain, but in the United States, after the first wave of somewhat too optimistic and some extremely pessimistic reports, it has been accepted as being the most valuable chemotherapeutic substance available at the present time for the treatment of neurosyphilis.

Tryparsamide is a pentavalent arsenical. It is a white, odorless, crystalline substance, readily soluble in water, yielding a neutral, stable solution. It is remarkably nonirritating to tissues, as compared with the trivalent arsenicals, producing very little discomfort or effect when it is accidentally allowed to escape from the vein into the surrounding tissues. It has been given intramuscularly but this method of administration is not recommended. Abscesses have been observed to occur after intramuscular injection (Solomon and Viets) (143). It differs from arsphenamine in being a much less effective spirocheticide and in having no effect upon the virus of rat bite fever or on inoculation malaria (Solomon, Epstein, and Berk) (148). One of the theories advanced to explain its effectiveness in neurosyphilis is that it stimulates metabolism as evidenced by the gain in weight of patients and animals treated with it.

Either immediate or late reactions are extremely rare as compared with other arsenicals used in the treatment of syphilis. Some untoward effects of tryparsamide have, however, been reported. These include nausea and vomiting, which as a rule do not occur immediately after the injection. They are noted more often 5 to 10 hours later—Cole (24), Cormia (26), Crawford (28), Silverston (136), Solomon and Viets (143), Wile and Wieder (169). Others are short periods of mental confusion with aggravation of the symptoms of general paresis—Cocke (23), Hoverson (59), Schoch (128), Silverston (136), Solomon and Viets (144), Stokes and Wilhelm (156)—and elevation of temperature to 103–104 degrees—Crawford (28).

Fifteen authors have reported the occurrence of jaundice, usually mild, in a total of 31 cases—1, Cocke (23), 1, Cormia (26), 2, Crawford (28), 2, Ebaugh and Dixon (34), 1, Golz (49), 3, Jaenike and Forman (63), 3, Keith and Le Marquand (65), 2, Moore (98), 1, Nomland and coworkers (105), 1, O'Leary and Becker (106), 2, Silverston (136), 6,

Soffer (141), 2, Solomon and Viets (144), 1, Wile and Wieder (169), 3, Wile and Sams (167).

Nitritoid reactions—1 case, Astrachan and Franks (1), 1, Cormia (26), 1, Lichtenstein (79), 1, Miller and O'Donnell (94), 1, O'Leary and Becker (106), 1, Silverston (136); Herxheimer reactions—1, Cormia (26), 2, Ebaugh and Dixon (34), 1, Stokes and Wilhelm (156); edema—1, Crawford (28), 1, Solomon and Viets (143); intolerance characterized by loss of weight and mental confusion—3, Schoch (128); hemorrhagic disease—1, Moore, Robinson and Keidel (95); conjunctivitis—3, Silverston (136); onychopodosis after 1 injection—1, Silverston (136), and albuminuria with a 50 percent eosinophilia and an associated dermatitis—1, Bragman (8) have also been observed following the administration of tryparsamide.

Sterile abscesses may develop if the drug is injected intramuscularly—2 cases, Solomon and Viets (143). Twenty cases of dermatitis due to tryparsamide have been reported in the literature—1, Bragman (8), 1, Cole (24), 1, Ebaugh and Dixon (34), 1, Ellis (37), 1, Golz (49), 2, Keith and Le Marquand (65), 1, Kemp and Menninger (66), 1, Lichtenstein (79), 1, Nair (102), 1, O'Leary and Becker (106), 1, Phelps (113), 1, Pillsbury (115), 4, Robinson (120), 1, Robinson (121), 1, Rosenberg (122), 1, Soffer (141).

Apparently reactions to tryparsamide are increasing in frequency and severity. Attention is called to this fact in a recent editorial (35). Traenkle and Dolee (162) have recently reported two cases of acute fatal liver necrosis following the administration of tryparsamide. The increased toxicity of this drug is thought to be due to some variation in the raw materials used or to a slight change in the method of manufacture which has occurred inadvertently. Merek and Co., who manufacture the drug, are attempting to determine the cause of its increased toxicity.

The injurious effect of tryparsamide on the optic nerve was observed during its first clinical application by Pearce (111) who used it in the treatment of trypanosomiasis. Among a total of 77 cases treated there were 17 instances of visual impairment of which 6 were slight, 7 moderate, and 4 marked. Ten of these completely recovered, whereas 3 retained moderate and 4 slight impairment of vision. Transient visual disturbances occurred, therefore, in 22 percent and permanent damage in 9 percent of the cases. The dosage varied between 0.5 and 7.0 gm. The visual disturbances were observed to occur chiefly in patients with marked alteration of the spinal fluid.

Lorenz, Loevenhart, Bleckwenn and Hodges (83), who were the first to make a systematic study of the drug in the treatment of central nervous system syphilis, at first used 5 gm. doses at weekly intervals and found that after 4 to 5 weeks about 40 percent of patients complained of dimness of vision. Smaller doses were then tried and it was found that a weekly dose of 3 gm. was therapeutically effective and produced visual symptoms in a much smaller number of cases.

Woods and Moore (171) made a careful study of the visual disturbances produced by tryparsamide in a series of 241 patients who received more than 3,000 injections of the drug which was administered in weekly doses of 3 gm. in a course of 8 to 16 injections. They classified visual disturbances into subjective and objective. The subjective type of reaction is without definite objective ocular findings or visual field changes when examined at the height of the reaction or at any other time. The visual disturbances are remarkably similar. From 6 to 24 hours after the injection a dazzling sensation appears, at times associated with a "tremor in the air." The sensation is described as exactly like that produced by looking at snow in intense sunlight.

In dim light these symptoms disappear or are greatly diminished; in strong light they are increased. Their duration is inconstant, ranging from 1 or 2 days to 2 weeks. From the ophthalmologic standpoint there is no external change in the eyes and no diminution of vision. Muscular balance and accommodation are not affected. The media and fundi show no essential change but in a few instances a low grade hyperemia of the fundus is observed, without, however, any blurring of the neuroretinal margins or alteration in the physiologic cups. This hyperemia if present, is always rather indefinite and transient, often disappearing within 24 hours. There are no changes in the visual fields and blind spots and no scotomas, either absolute or relative. In the objective type of reaction the same symptoms of dazzling vision are present, and are usually but not necessarily more intense than in the subjective group. The symptoms appear about 15 hours after treatment and are usually accompanied by a slight dimness or veiling of vision. Objects in dim illumination appear gray to the patient. On ophthalmologic examination nothing is found externally. Frequently, however, there is a slight but definite diminution of vision. The fundi are usually normal although occasionally the same hyperemia of the nerve head and retina is observed. In the visual fields there are remarkable changes consisting of concentric contraction of the form fields, affecting particularly the nasal, upper, and lower fields. The temporal field is involved last or not at all. The color fields remain unaffected.

Changes in the blind spots or scotomas of any type which could be attributed to the action of tryparsamide were never observed. In a few of the more severe cases visual failure and field contraction slowly increased to a maximum within 3 weeks but except in 1 case stopped well short of blindness. It was observed by these authors that 80 percent of all visual reactions occurred between the first and the fifth dose and 94 percent of reactions between the first and the tenth dose. (This observation has been since

confirmed by all other authors.) They stressed the importance of careful observation of the eyes early in the course of treatment since in the majority of cases the drug can be safely administered if the first 5 doses are well tolerated. They found that objective damage may occur even if small doses of tryparsamide are given. Although the majority of eye reactions occurred in patients with neurosyphilis, there were 6 cases of ocular damage in patients without neurosyphilis. Three of these patients had late syphilis with no clinical or serologic evidence of involvement of the nervous system, 2 had postencephalitic parkinsonian syndromes. Mild subjective reactions developed in these patients, and in a nonsyphilitic boy with lymphosarcoma a transitory high degree of visual impairment developed. In the neurosyphilitic group patients with general paresis and tabes were the most prone to ocular reactions. In 19 (22.8 percent) of 83 patients with general paresis and tabes some degree of visual impairment developed, while of 85 patients with other types of neurosyphilis impairment developed in only 3 (15.2 percent). In 65 patients in whom central nervous system disease could be excluded, the incidence of downward visual phenomena was only 6.1 percent while in 180 cases of neurosyphilis and postencephalitic parkinsonian disease it was 21.1 percent. There were 110 patients whose eyes were examined before and during the treatment by a competent ophthalmologist and for whom accurate records of the objective condition of the eyes, visual acuity, and visual fields were kept. In 95 there was complete absence of any preexisting ocular lesions. Following tryparsamide therapy visual disturbances developed in 9 of these patients (21 percent). The other 15 patients had definite preexisting syphilitic lesions of the eyes and in 12 of these the optic nerve was involved. Visual disturbances occurred in 4 (33 percent) of these 12 patients. The incidence of noteworthy permanent visual damage was 2.8 percent of the 241 cases.

Sloan and Woods (142) made a care-

ful follow-up study of 16 patients who had objective ocular reactions after treatment with tryparsamide. Ten of these patients were observed for a period of 9 months to 10 years. All of these patients had normal optic nerves, normal vision, and normal visual fields before tryparsamide was given. Two types of objective reaction to tryparsamide were observed to occur—acute and chronic. The acute type which occurs only rarely is characterized by rapid loss of vision resulting in almost complete blindness. This is followed by gradual improvement in central vision and widening of the fields. The more frequent chronic type of reaction is characterized by subjective visual symptoms of a milder degree than those occurring in an acute reaction. There may be little or no reduction in the central acuity of vision and no visible change in the fundi so that the evidence of objective ocular damage is confined chiefly to the changes in the visual fields.

Among the 16 cases 1 patient showed an acute reaction. Tryparsamide was administered to 2 of these 16 patients in spite of subjective symptoms, to determine whether or not objective changes would occur. Optic atrophy resulted in both cases. The remaining 13 had typical reactions of the chronic type, and they illustrate the course taken by this reaction when tryparsamide is permanently discontinued at the first appearance of objective changes. Nine of the 13 patients had subjective symptoms as early as the third dose. In 2 of the 4 cases with late subjective symptoms the first reaction produced no objective ocular changes. Tryparsamide was therefore resumed until a second reaction occurred. This reaction was followed in 1 case by moderate contraction of the fields in both eyes and in the second case by slight contraction in 1 eye only. Two patients had slight pallor of the disks in both eyes and 1 patient had slight pallor in 1 eye only. In the other 10 there was no visible evidence of atrophy in either eye. In none of the 13 patients was there any reduction in central vision as a result of the reaction

to tryparsamide. The field defects were classified as marked, moderate, and slight. Moderate contraction occurred much more frequently than either the slight or the severe impairment. Marked contraction occurred in only 3 cases. Nine of the 13 had moderately contracted fields for 1° white in one or both eyes. This was associated with normal visual acuity in every case and with normal nerve heads, except in 1 patient who had a questionable pallor of both disks. All of the fields had the same general shape with the greatest contraction in the upper, lower, and nasal fields with relatively little contraction in the temporal field. There was a much less marked effect on the 1° blue and red fields than on the 1° white fields. In a majority of the cases the limits of the color fields fell within the normal range and contraction could be proved only by comparison with the fields measured prior to the administration of tryparsamide. During the period of observation 1 patient showed no further change in the visual fields, 6 showed improvement or complete recovery, 3 showed decrease in extent of the fields later followed by a gradual improvement. In every case the final fields were the same or better than those found immediately after the reaction to tryparsamide. One patient whose disks were normal immediately after the reaction had a questionable pallor of both disks at the end of 18 months. Two patients had slight reduction in visual acuity. There were 2 cases in which tryparsamide was continued in spite of warning subjective symptoms and without retesting for signs of objective damage. One of these retained normal vision and had only moderately contracted fields; the other progressed to complete blindness. Both patients ultimately had optic atrophy, slight in the first case and well advanced in the second. In 6 of the patients there was a decreased sensitivity to light. In 10 the dark adaptation curves were within the normal range. A correlation of these findings with the visual field changes showed that a reduction in sen-

sitivity to light occurred in every eye with marked contraction of the fields and in every eye with pallor of the disk. In general the light sense was normal in the less severe reactions and was reduced in those patients with marked contraction of the fields.

A comparison between the field defects characteristic of a tryparsamide reaction and those of syphilitic optic atrophy reveals similarity in certain respects. In both there is a greater contraction of the limits for 1° white than for 1° blue and red and in the early stages a greater defect for red than for blue. The field defects found in syphilitic optic atrophy do not show the relative sparing of the temporal field which is found consistently in the objective reactions to tryparsamide. In more than 50 cases of primary syphilitic optic atrophy uncomplicated by a reaction to tryparsamide the authors never encountered a single case with visual field changes similar to those here reported.

The authors, therefore, do not believe that the visual field defects accompanying tryparsamide administration are due to a reactivation of a latent syphilitic optic atrophy. They conclude from these observations that, in patients with normal optic nerves, fields, and vision prior to the administration of tryparsamide, there is little danger provided the drug is permanently discontinued at the first appearance of visual field defects. Continuation of the drug may result in serious visual damage or total blindness.

There is some difference of opinion as to how tryparsamide affects the optic nerve. Some believe that its effect is a direct toxic action and others that it activates the syphilitic process or causes its extension into the optic nerve. In favor of the latter assumption is the observation that eye involvement occurs more frequently when there is a pre-existing lesion of the optic nerve. Sézary and de Font-Réaulx (134), who have published a review of the literature on the ocular complications of pentavalent arsenicals, are convinced of the direct toxic action of tryparsamide. In

support of their view are the clinical observations of optic atrophy occurring in patients treated with atoxyl and trypanosomiasis, increased danger with large doses too frequently given, bilateral involvement of the optic nerve, the histologic findings of degenerative rather than inflammatory lesions, and the fact that these changes can be reproduced in animals by giving them pentavalent arsenicals. Whatever the mode of action of trypanosamide may be, the practical importance lies in the fact that in a certain percentage of cases serious damage to the optic nerves does occur.

Young and Loevenhart (173) made ophthalmoscopic examinations of the eyes of rabbits before and after the administration of various trivalent and pentavalent arsenicals. In the animals to whom trypanosamide had been administered it was observed that after the fourth dose there was edema of the optic disks. After 5 months there was a hemorrhagic exudate in the vitreous. Among the compounds studied, it was found that those trivalent and pentavalent organic arsenicals which had an amino group or a substituted amino group in the para position to the arsenic produced optic lesions in the rabbit. Organic arsenicals with the amino group or substituted amino group in the ortho or meta position to the arsenic produced no optic lesions in the rabbit.

Lazar (76) made weekly injections of trypanosamide into rabbits, beginning with 0.2 gm. and 0.6 gm. and increasing by 0.1 gm. until 0.5 gm. and 1.4 gm. respectively were given. Microscopic examination revealed no changes in the nervous elements of the retina. One rabbit was given 1.5 gm. and killed after 10 days. Microscopic examination showed no marked changes in the eyes except a mild edema of the iris. There were, however, multiple small foci of perivascular hemorrhage in the chiasm and throughout the substance of the brain. The axillary cylinders near such foci in the chiasm were swollen and showed some disinte-

gration. There was an extensive hemorrhage in the outer sheaths of the optic nerve with a beginning mesenchymal reaction of repair. Two more rabbits were injected and showed similar changes. The author states that it cannot be said with any degree of certainty that these changes observed after injection of the drug were due to it. Histologic examination of the brain and of the eyes from a patient with syphilis in whom sudden blindness had developed following the administration of trypanosamide 2½ years before death was also made. The optic nerves were atrophic and had a marked increase of intraneural connective tissue and proliferation of the surrounding pia arachnoid. The optic tracts were atrophic with complete absence of myelin and mild glial proliferation. There were multiple organized foci of softening in the occipital cortex, chiefly around the larger blood vessels. Histologically these foci suggested former multiple hemorrhages which had become organized. The author concluded that the optic atrophy was probably syphilitic in origin whereas the multiple cortical foci might have been produced by the toxic action of trypanosamide.

Leinfelder (78) studied the brain and optic nerves of a 53-year-old tabetic with early optic atrophy in whom blindness developed after the administration of a single dose of 1.0 gm. of trypanosamide and who died of uremia 9 days after he had been given the injection of trypanosamide. No changes could be observed in the occipital cortex and the lateral geniculate bodies. There was no inflammatory reaction of the optic nerves but there were degenerative changes characteristic of optic atrophy. In the retina acute degeneration of the retinal ganglion cells was observed. It is possible that these retinal alterations may have been post-mortem changes in view of the fact that Stargardt (152) found that normal conditions of the retina could be maintained only when the eye is injected with a fixing solution (he used Birch-Hirschfeld mixture) not later

than 20 minutes after death. The autopsy in this case was performed 2 hours after death.

The manner, therefore, in which tryparsamide affects the optic nerve remains obscure. Some patients seem to have a definite idiosyncrasy to the drug, a single small dose producing marked visual disturbances or even blindness.

Based on the early observations in the use of tryparsamide that the optic nerve is much more likely to be damaged by the drug when there are preexisting ocular lesions, its use in the presence of optic atrophy was considered to be definitely contraindicated. Some physicians, however, have ventured to use the drug in such cases and some of them have been optimistic about their results. Among such enthusiasts is Mayer (87, 88). He administered tryparsamide to a group of 15 patients with syphilitic optic atrophy. In three of these objective findings developed. In 2 the condition returned to normal but in the third contraction of the fields was permanent. Ten of these patients were reexamined 5 years later. At this time 1 had a decrease in the visual field, 2 had an increase in the visual field, 9 "eyes" had increased visual acuity and 2 "eyes" had decreased visual acuity. He reports a high percentage of increased visual acuity following treatment with tryparsamide. It is a question if this might not have been due to general improvement in the mental status of the patient. Neff (103), who also observed improvement in visual acuity following tryparsamide attributed it to general improvement and better cooperation on the part of the patient. Mayer, too, recognizes the direct ocular effect of tryparsamide when he cites a case in which, following 6 injections of tryparsamide, the fields in a patient observed were reduced to 5° of the center in both eyes. Visual acuity was not reduced. However, he believes that "the low incidence of damage fully justifies the use of tryparsamide with proper observation." Lillie (80) also is of the opinion that the use of tryparsamide is not contraindicated by patho-

logic changes in the fundus. In support of this view he reports having treated with tryparsamide 114 cases of syphilis "with ocular changes." In this group only 3.5 percent of permanent damage to the optic nerve as result of the treatment was observed, whereas among 97 cases treated with arsenicals other than tryparsamide fundus changes developed in 9 percent and perimetric field disturbances in 20 percent. He states that ocular changes occurred as often with arsphenamine as with tryparsamide. These findings are not in agreement with those of other authors (98). Lillie (81) also reports the finding of marked, "slit-like" contraction of the visual fields in patients who were given tryparsamide for years, but he disregards any possible effect of the drug and attributes this finding entirely to the syphilis.

O'Leary and Becker (106), who accept Lillie's hypothesis that syphilis and not tryparsamide is frequently the factor involved in visual complications, state that their experience does not permit them to ignore subjective complaints or to continue treatment unhesitatingly when such complaints are present. They find that in most cases the subjective complaints are transient but, occasionally, if treatment is continued it will result in permanent damage. Their cases in which the contracted fields were permanent were all of the tabetic type.

Neff (103) who administered tryparsamide to 15 patients with optic atrophy, observed visual field contraction in 26.7 percent of cases but hesitates to incriminate the drug, saying that perhaps it was a result of the disease itself. He believes that the presence of syphilitic changes in the optic tract do not constitute an absolute contraindication to tryparsamide and that the probability of clinical improvement apart from the vision should be considered since the hazard to the eyes is great whether treated or untreated.

Cady and Alvis (17), who observed only 1.3 percent of permanent damage to the optic nerves in patients treated with tryparsamide who had normal optic

nerves before they were given the drug, found that 37 percent of patients with optic nerve involvement had definite progression of the lesion after they had been given tryparsamide. They conclude from this that patients with optic nerve involvement are more liable to injury by the treatment than normal patients but that they show favorable response to treatment if it is properly controlled. They advised that the occurrence of subjective symptoms should be followed by an investigation for objective signs. If no objective signs are found, tryparsamide may be continued with caution. With objective findings tryparsamide should be stopped for at least a month and then it may be resumed.

Lees (77) who treated a group of 500 patients with neurosyphilis and normal optic nerves with tryparsamide reports an incidence of permanent damage of 1 percent in this group. He also treated a group of 21 patients with optic atrophy with tryparsamide. In 5 of these cases the subjective symptoms were so severe and continuous with the first few injections that the drug was stopped. In 2 (9.5 percent) there was such rapid deterioration of vision that it was considered to be due to a direct action of the drug. No case was observed, even among those with less marked optic atrophy, in which there was a lessening of the objective signs of atrophy as a result of treatment. This also has been the observation of Neymann and Singleton (104) who treated 3 cases of primary optic atrophy with tryparsamide. Before treatment was given sight was practically limited to counting fingers held directly in front of the eyes. These 3 patients were given 40, 32, and 24 injections of the drug. The vision remained stationary in each case, although the serologic findings improved in 2 of them. Gerbaux (47) reports treating a woman who had general paresis and optic atrophy with tryparsamide which resulted in slight improvement of vision. Ophthalmologic examination apparently was not made.

Cormia (26) treated only 2 cases of optic atrophy with tryparsamide. One patient who was almost completely blind when first seen was unaffected by either 20 Swift-Ellis treatments or by 50 injections of tryparsamide. The other who had moderately advanced atrophy suffered marked field constriction after being given 0.5 gm. of tryparsamide, although he previously had had months of preparatory treatment with bismuth. Tryparsamide was discontinued and the fields returned to the condition in which they were found before treatment. The author concludes that tryparsamide therapy of optic atrophy is still in the experimental stage and should be carried out cautiously if at all.

Lazar (76), whose patients are included in the series reported by Mayer (at the Northwestern University Clinic), made ophthalmoscopic examinations on patients who were being treated with tryparsamide for syphilis of the central nervous system. Optic atrophy was a contraindication to treatment in this series but a few exceptions were made to this rule. Of the total number of 32 persons, 2 had permanent loss of vision, and 3 had constricted fields and reduction in vision from which they recovered. The changes were seen after the first, second, and third injections. In only 3 cases could it be positively determined that the atrophy was due to the drug. Two cases are cited, one in which the patient had optic atrophy before treatment was given and the other in which tryparsamide was resumed 2 weeks after a slight constriction in visual fields had been noted. In both cases the drug produced a marked decrease in vision and visual fields, which improved slightly in the first and to a greater extent in the second case. The author concludes from his observations that tryparsamide has a definite toxic effect on the visual apparatus of certain patients which may cause serious and permanent damage to a previously normal visual apparatus. He states that optic atrophy or constricted fields are positive contraindications to injection of the drug. The interesting

fact is that two different authors (Mayer and Lazar), observing the same group of patients, reach almost opposite conclusions, for, although Mayer is aware that tryparsamide may cause damage to the optic nerve, he minimizes its danger. The difference in conclusions seems therefore to arise not from the difference in findings so much as from the interpretation placed upon them by the various observers.

Fine and Barkan (41), who made careful ophthalmoscopic observations in a group of 132 patients being given tryparsamide for neurosyphilis, found objective changes as a result of the treatment in 8.3 percent and permanent damage in 2.3 percent of cases. They state that the administration of tryparsamide carries a distinct hazard which is probably increased by the presence of pre-existing damage to the optic nerve, notably tabetic optic atrophy. This hazard can be reduced to a minimum by the adoption of a rigid routine for the examination of the patients' fields, vision, and fundi by an ophthalmologist.

In a series of 262 cases of general paresis treated by Bookhammer (7) there were 26 whose optic disks were slightly off-color but which showed no evidence of atrophy of the optic nerve. With treatment, 34.6 percent of these developed subjective and objective signs of atrophy of the optic nerve. Of the remaining 183 patients whose eyegrounds were normal, atrophy of the optic nerve developed in 5.4 percent.

Suker (159) cautions against the use of tryparsamide in any type of optic nerve involvement in syphilis. Ellery (36) agrees with Lillie that changes are due to syphilis rather than to tryparsamide but he does not give tryparsamide to patients with optic atrophy. Menzies (91, 92) believes that optic atrophy is a great contraindication and a very serious one to treatment with tryparsamide. Kahn (64) states that symptoms of optic atrophy are not always a contraindication to its use. Neymann and Singleton (104), although they noted no improvement in cases of optic atrophy treated

with tryparsamide, feel that the possibilities of eye complications are not grave. Crawford (28) states that tryparsamide should not be used when serious abnormalities are found. Bluemel and Greig (6) noted sudden blindness after tryparsamide in a young paraplegic man with pallor of the optic disks before treatment. Hindman (56) cites the case of a paretic who had a reaction to tryparsamide. When the drug was again given after a rest period the result was total blindness. Solomon and Epstein (145) state that they are not satisfied with the explanation that damage of the optic nerve is due to a reactive process in the interstitial tissue due to too rapid stimulation by the drug and accept the original hypothesis that it is an arsenic damage. Wagener (166) states that the incautious use of tryparsamide in the treatment of neurosyphilis may result, in a certain percentage of cases, in serious damage to the optic nerve. Prompt discontinuance of the drug on the appearance of the first signs of organic involvement of the optic nerve will in most cases prevent the development of progressive and permanent loss of vision. Lorenz, Loevenhart, Bleekwen and Hodges (83) advise that every patient should have a careful ophthalmoscopic examination before tryparsamide is given and in any case showing retinal changes the drug should be used with great caution. Cordes (25) feels that atrophy is no contraindication but that tryparsamide should not be used in optic neuritis. His patients were carefully examined in the eye clinic before treatment was instituted and following each of the first 6 injections. In only a few instances did field changes occur that warranted discontinuance of the drug. Where symptoms appeared the drug was stopped for 3 to 4 months and then in almost every case it could be tolerated. There were no cases of loss of vision in his series that could be attributed to tryparsamide. Hadden and Wilson (51) state that the danger to vision has been greatly overemphasized. Ebaugh and Dixon (34) considered optic atrophy in any degree

a definite contraindication to the use of tryparsamide. Roth (123) and Muncey (101) are on the side of those minimizing the dangers of tryparsamide. P. de Font-Réaulx (43) states that lesions of the optic nerve contraindicate the use of tryparsamide. Reese (119) differentiates between stationary neuritic atrophy and slowly progressive tabetic optic atrophy on the one hand, in which he states that tryparsamide should be given, and malignant advanced and progressive optic atrophy on the other hand in which tryparsamide is contraindicated.

Finally, Moore, (97) who together with Woods (171) was the first to make a careful and systematic study of tryparsamide in neurosyphilis, especially in relation to the optic nerve, states in his discussion of the syphilitic optic atrophies that his observations indicate that tryparsamide is more likely to produce visual damage in patients in whom the optic nerves are already actually (or potentially) diseased than in normal individuals. He and Woods observed untoward visual reactions from the use of tryparsamide in 21 percent of patients with neurosyphilis and in only 6 percent of patients in whom central nervous system disease could be excluded. Among patients with neurosyphilis reactions occurred in 23 percent of those with tabes and paresis and in only 15 percent of patients with other forms of neurosyphilis. In a group of 12 patients with optic atrophy treated with tryparsamide, visual damage developed in 4 (33 percent). One of these patients with slowly progressive optic atrophy of moderate degree was precipitated into sudden blindness after the second dose of the drug. Woods and Moore did not observe any noticeable improvement in these cases of optic atrophy treated with tryparsamide. This observation has been made by a number of other authors as cited above. In regard to those who report improvement in optic atrophy as a result of treatment with tryparsamide one might consider what Behr (3) says in regard to the treatment of tabetic optic atrophy.

He states that it is difficult in tabetic optic atrophy to evaluate the effectiveness of therapeutic measures, at least insofar as a causal relationship between the therapy and a slowing up of the process of degeneration of the optic nerve is concerned. As is true of other tabetic symptoms, optic atrophy may have longer or shorter remissions without any recognizable or demonstrable cause. Since the cases associated with optic atrophy are usually mild in type such remissions and apparent improvements are to be expected. Spontaneous regression, though more rare than spontaneous remission, also occurs and the patient may have sudden loss of vision. Such cases, however, are rare exceptions. Loss of vision in the course of 2 to 3 months is extremely unusual. Moore summarizes his position in saying that, since other methods of treatment (subdural or fever therapy) are more likely to produce good results and since tryparsamide is potentially dangerous even to the normal eye, its use in optic atrophy should be avoided unless other features of the individual case seem to render its use imperative or unless the atrophy is already complete and the patient blind. If the drug must be used in a patient who still retains some vision it should be done only under the most painstaking ophthalmologic control.

Stokes, in discussing Lazar's report (76) on the ocular complications following tryparsamide states that it is not at all impossible that the injury to the optic nerve is the result of a localized flare-up of the disease (Herxheimer reaction) at some point in the optic tract yet to be identified. This might lead to localized destructive edema followed by atrophic changes. He outlines the following preventive measures to be employed with tryparsamide therapy. The eyes should be examined before the first injection and on the third day after each subsequent injection up to the sixth to tenth day. The confused patient who cannot answer accurately in tests of the fields or cannot report his subjective symptoms of clouding, dazzling and blur-

ring promptly and accurately is an increased risk. The vital ophthalmologic tests are those of fields and visual acuity and not the fundus examination, in which no change may appear until weeks after all damage is done. Subjective symptoms rather than objective signs, however, furnish the real warnings. The drug should be immediately and completely discontinued on the first appearance of objective signs of damage.

In regard to the treatment of trypanamide amblyopia, the only procedure that is carried out, as a rule, is the immediate withdrawal of the drug as soon as symptoms occur. Casten (21) reports the case of a 59-year-old patient with neurosyphilis who became blind after the second injection of trypanamide. Forced drainage of the cerebrospinal fluid was followed by rapid and marked improvement in vision. Examination of the fundi showed marked pallor of the disks of both eyes. Mawas and Pinheiro (86) report a patient with neurosyphilis in whom loss of vision except for light perception developed after the eighth injection of a course of trypanamide (he had been treated with trypanamide and bismuth for several years). He was given injections of acetylcholine three times weekly and drops of pilocarpine solution were instilled into the eyes every evening. He completely regained vision in 3 days but examination revealed pallor of the disks and contraction of the visual fields. The authors state that, although they do not discard the theory of the toxic effect of the drug, they believe that in this particular case an arterial spasm occurred which was relieved by acetylcholine.

In summarizing the results of treatment of neurosyphilis in relation to its effect on the optic nerve based on the observations of various authors, it is seen that the average amount of permanent damage to the optic nerve in cases in which there was no involvement prior to treatment amounts to 2.9 percent. The much greater incidence of ocular complications in cases with optic atrophy which were treated with trypanamide is

apparent from the results of table 1 which shows an average incidence of 22.7 percent of permanent optic nerve damage for this group.

TABLE 1.—Patients with neurosyphilis treated with trypanamide showing effect of drug on optic nerve

Year studies reported	Total patients	Status of optic nerve before and after treatment with trypanamide			
		Normal optic nerve		Partial optic atrophy	
		Patients treated	Percent with permanent optic nerve damage after trypanamide	Patients treated	Percent with permanent optic nerve damage after trypanamide
1923.....	93	93	-----	-----	-----
1924.....	486	486	0.9	-----	-----
1925.....	543	520	3.1	23	27.6
1926.....	689	659	2.7	30	33.0
1927.....	183	183	1.8	-----	-----
1928.....	174	174	.7	-----	-----
1929.....	140	140	.8	-----	-----
1931.....	140	140	-----	-----	-----
1932.....	560	539	.5	21	9.5
1934.....	194	178	3.0	16	6.7
1936.....	249	223	6.5	26	34.6
1937.....	172	172	13.6	-----	-----
1938.....	76	76	4.0	-----	-----
Total	3,699	3,583	2.9	116	22.7

THERAPEUTIC USE OF TRYPARSAMIDE IN SYPHILIS

The first study of trypanamide in the treatment of neurosyphilis was made at the suggestion of Wade H. Brown of the Rockefeller Institute by Lorenz, Loevenhart, Bleckwenn and Hodges (83) of the University of Wisconsin who began their study in 1919. Trypanamide was first used in 5 gm. doses given intravenously but since after 4 to 5 doses about 40 percent of patients complained of dimness of vision, it was decided to reduce the dose to 3 gm. This amount given once weekly was found to be therapeutically effective. Besides trypanamide, mercury salicylate in 1 grain doses was given intramuscularly once weekly. These drugs were administered in courses of 8 injections of trypanamide and 9 injections of mercury. After a rest period of from 5 to 8

weeks, a second similar course was repeated and, if necessary, a third course. Among the cases of neurosyphilis which were treated there were 42 patients with far advanced general paresis. Twenty-one of these had complete remissions and were able to return to work. (Practically all authors have accepted the terminology of "remission", "improvement", "no improvement", as first used by Lorenz, Loevenhart, Bleckweinn and Hodges. By "remission" is understood that the patient is able to return to work and to perform tasks requiring the same, or almost the same, amount of skill as the work which he did prior to the onset of the disease.) Among 12 patients with early general paresis the disease could be completely arrested in 7. A definite effect of tryparsamide on nutrition was observed. Most of the patients gained weight and were improved in general health. Five cases of tabes were treated, with 4 remissions and 1 improvement. In 1 of the arrested (late) cases the blood and spinal fluid findings became completely negative. In the others the blood serologic test became negative and the spinal fluid findings were reduced. Five cases of taboparesis were treated, with 4 remissions and 1 improvement. There was also considerable improvement in the serologic findings in these cases. Of the 10 cases of meningovascular syphilis, 9 recovered completely. The most marked changes in the serologic findings were seen in the blood Wassermann reactions and in the cells and globulin of the spinal fluid. The Wassermann reaction of the spinal fluid and the colloidal gold reaction changed more slowly.

The remarkable results obtained by Lorenz and his coworkers in the treatment of neurosyphilis were almost duplicated by those obtained by Moore, Robinson and Keidel (95) in a similar study. These authors included in their series 8 cases of early syphilis and found that in therapeutic doses tryparsamide had no effect on the lesions of early syphilis, and that it was not able to

destroy spirochetes in these lesions. They concluded that it is of no value as a spirocheticidal agent. They also observed practically no effect on cutaneous nodules and gummas or on the blood Wassermann reaction of 24 cases of late syphilis. The results obtained with 5 patients with cardiovascular syphilis were inconclusive. The authors also treated 3 cases of early neurosyphilis with tryparsamide. In 2 of these the diagnosis was based on positive spinal fluid examination alone. The cell count of the spinal fluid was reduced to normal in 1 case and was markedly reduced in another. Neither patient developed clinical signs of neurosyphilis during the period of treatment but in 1 of them a recurrent secondary skin eruption appeared on the day of the twelfth injection of tryparsamide. The third patient who had eighth nerve involvement and who had shown improvement with arsphenamine became worse after 1 injection of 1 gm. of tryparsamide. The authors advised against the use of tryparsamide in early neurosyphilis because the disease process is an acute reaction to the presence of spirochetes. There is often involvement of the auditory nerve and hearing can be preserved only by prompt treatment with powerful spirocheticidal drugs. In the treatment of late neurosyphilis these authors gave tryparsamide in courses of 6 to 18 injections followed by a period during which the patient took mercury rubs. A total of 27 cases of parenchymatous neurosyphilis and 10 cases of meningovascular syphilis was treated. The results compare very closely with those obtained by Lorenz and coworkers except in one particular. Whereas Lorenz and coworkers obtained a negative or less strongly positive blood serologic reaction in 98.6 percent of cases treated, Moore and his coworkers obtained this result in only 26.6 percent of their cases. There were 66.6 percent of clinical remissions among the parenchymatous neurosyphilis group and 90 percent among the meningovascular neurosyphilis group.

Lorenz, Loevenhart, Reitz and Eck (84) reported on the results of treatment of a total of 185 cases of neurosyphilis, some of which had been treated and observed since 1922. Their series included 84 patients with general paresis having (with the exception of 9 patients) only mild mental symptoms. Of this group 37 (41 percent) were mentally restored, 38 (42 percent) were improved, 9 (10 percent) were unchanged and 6 (7 percent) progressed. Among 6 cases of general paresis with atypical serologic tests 1 recovered and 5 showed some improvement in their mental condition. In a group of 23 cases of asymptomatic paresis the blood Wassermann reaction became negative in 1 and was improved in 6 cases. The cell count became normal and the globulin tests became negative or only slightly positive. The spinal fluid Wassermann reaction either became completely negative or a positive reaction was obtained only with large amounts of fluid. The colloidal gold curve changed from the paretic to the meningovascular type. It usually remained positive longer than the Wassermann reaction. In 12 cases lumbar puncture could not be obtained. In 4 cases there was practically no change in the blood or spinal fluid after 16 injections of tryparsamide and mercury. Among 14 cases of taboparesis there were 21 percent of remissions, and 50 percent were improved. Those showing remission clinically also showed the greatest serologic improvement. Of a total of 29 patients with tabes who had severe gastric crises and were treated with 32 to 40 injections, 10 (34 percent) were greatly relieved. In 55 percent treatment was without effect.

Lorenz (85) in 1928 reviewed the cases treated by the Wisconsin group in 1919-21. He found that the results obtained from the use of tryparsamide and mercury were permanent for at least 5 or 6 years. He was able to obtain reliable information in regard to 317 patients of the original group. Of these, 152 patients had recovered following treatment

in 1919 to 1921. Of this number 134 (87 percent) remained in good condition. It was noted that the recovered patients were about 7 years younger than the unimproved, that the disease was of shorter duration in the recovered group, and that the results were best in the excited or agitated patients. No definite clinical or serologic symptom complex was constantly associated with either good or poor prognosis. Some cases were slow in their response but with persistent effort they finally showed improvement and sometimes recovery. The author advised that at least 150 gm. of tryparsamide be given to each patient.

Reese (119) in 1933 discusses this same group of patients and also cautions, as does Lorenz, against the use of the drug in less than 1 gm. doses because small amounts seemed to intensify rather than alleviate symptoms. Among 314 patients with general paresis he noted remissions in 54 percent and in a group of 306 cases of meningovascular syphilis, clinical or serologic cures in 78 percent. Lancinating pain, urinary disturbances, and impotence were often relieved by treatment. He reported the following serologic results: Blood—Wassermann negative in 49.2 percent, reduced in 35.6 percent; spinal fluid—Wassermann negative in 25.7 percent, reduced in 47.0 percent, and change of the paretic colloidal gold curve to a meningovascular type of curve. The cell count was changed to normal and there was a reduction in the globulin in most cases.

Ebaugh and Dixon (34) treated 52 cases of general paresis with tryparsamide in courses of 10 injections. Tryparsamide was the only drug used. Among this group which included 11 deteriorated patients, 28.8 percent were markedly improved, these patients being able to go back to work. In all cases the cell count and the globulin returned to normal limits after the first course. There was reduction in the colloidal gold curve but the spinal fluid Wassermann reaction remained unchanged in every case. Intraspinal and intracisternal try-

tryparsamide (Swift-Ellis technic) had little effect upon 3 patients, 2 of whom were given 10 injections.

Hadden and Wilson (51) reported in 1927 on these 52 patients first reported by Ebaugh and Dixon. Of this group 42 patients were followed and all remained in fairly good mental and physical condition. The clinical results surpassed the serologic improvement.

Solomon and Viets (143) report on the use of tryparsamide in 100 cases of neurosyphilis which were treated for about 11 months. They did not have a single case of parenchymatous neurosyphilis in which there was an entirely negative spinal fluid finding. The cell count almost invariably became normal after 6 to 8 injections; the globulin was reduced in a large number of cases but it rarely became normal. Among 71 cases of various types the spinal fluid Wassermann was changed from positive to negative in 12 (16.9 percent), reduced in 6 (8.5 percent), and unchanged in 53 (74.6 percent). Practically all the changes from positive to negative were in patients with tabes. The colloidal gold curve was slightly reduced in a number of cases and became negative in a few. They found tryparsamide to be more effective in reducing the cell count than either arsphenamine or subarachnoid injections although the same effect was obtained by subarachnoid injections over a longer period of time. Tryparsamide was not found to be more effective in general in reducing spinal fluid findings (except cell count) than other methods, except in certain cases of tabes. Good results were obtained with tryparsamide in the treatment of tabes; the results in other types of neurosyphilis were not remarkable.

Moore, Robinson and Lyman (96) reported on 133 patients with neurosyphilis who had been observed for 4 years. The clinical results in this group were obscured by the fact that a large number of the patients had been intensively treated just prior to tryparsamide therapy. The authors' estimate of the clinical effect of tryparsamide is based on the results obtained in 78 neurosyphilitic

patients of whom 49 had been previously treated and 29 had not. This group included 36 patients with general paresis among whom complete remissions occurred in 9. Clinical and serologic improvement did not necessarily parallel each other. Lightning pains and gastric crises were improved in 3 and completely relieved in 6 of 18 patients with tabes. In some of these, previous intensive treatment had failed to bring relief. No definite effect on ataxia was observed. The most striking clinical results were obtained in the meningovascular group. In 20 out of 24 of this group such symptoms as headache, vertigo, convulsions, and cranial nerve palsies were improved or completely relieved. The effect on the blood Wassermann reaction in neurosyphilis was found to be as negligible as it was in tertiary syphilis. The effect on the spinal fluid changes in neurosyphilis was found to be superior in degree and rapidity to that of any other form of antisyphilitic treatment. It was thought that this effect was more marked in those patients who had received previous intensive arsphenamine therapy. Of the entire group of 133 patients, 20 fulfilled the tests for clinical arrest with blood and spinal fluid serologically normal for 1 year. This group included 4 cases of tabes, 2 of general paresis, 2 of asymptomatic paresis, and 12 of meningovascular neurosyphilis.

Wile and Wieder (168), in their preliminary report presented the results of treatment of 50 neurosyphilitic patients with tryparsamide. Mercury and iodides were given between courses. The average amount of treatment was only 7 doses of 2 to 3 gm. of tryparsamide per patient. No appreciable changes in any of the cerebrospinal fluid reactions were observed with the exception of meningovascular syphilis in which a high cell count returned to almost normal with parallel changes in the other constituents of the fluid. There were no marked clinical improvements.

In their next report Wile and Wieder (169) extended their series to include 85 patients whose treatment consisted

of more than 800 injections of tryparsamide as well as mercury injections or inunctions and who were followed for about a year and a half. Among patients in the parenchymatous neurosyphilis group there were 26.8 percent of improvements. (Of the entire group, 24 were considered to be clinically improved—7 cases of general paresis, 2 of taboparesis, 2 of tabes, 12 of diffuse cerebrospinal syphilis, and 1 of acute basilar meningitis.) The cell count was reduced in 27.5 and the colloidal gold curve in 15.7 percent of cases. The spinal fluid Wassermann reaction became negative in 6 percent of cases. The colloidal gold curve became negative in 2 and was reduced in 6 percent of cases. Among the patients with meningo-vascular neurosyphilis there were 38.2 percent of improvements and the cerebrospinal fluid changes were somewhat more marked than in the parenchymatous group.

Stokes and Wilhelm (156) treated 152 patients who had various types of neurosyphilis with tryparsamide (3 gm. weekly doses in courses of 8 to 10 weeks) accompanied by intramuscular injections of mercury salicylate. Among the cases of early general paresis the symptomatic response was immediate and marked and was greater than the serologic response of both blood and spinal fluid. The effect of treatment on the serologic tests of the asymptomatic paresis group was not striking. The results were good in cases of tabes. The following "good" results were obtained with an average of 20 injections per patient: General paresis, 15 percent; early general paresis, 66 percent; neurosyphilis, including asymptomatic general paresis, 66 percent; tabes, 60 percent; and congenital neurosyphilis (3 cases), 33 percent. The blood serologic findings are more in agreement with those of Lorenz and coworkers than with those of Moore and coworkers. The spinal fluid Wassermann reactions show fewer complete reversals.

O'Leary and Becker (106) in 1926 reviewed the cases which were first reported by Stokes and Wilhelm in 1924,

with the exception of the group of patients with advanced general paresis who were treated at the Rochester [Minn.] State Hospital. To this number they added their observations since 1924. A total of 113 case histories was reviewed. Among the early general paresis group there were 12 percent of definite remissions, 66 percent were improved, and in 20 percent the spinal fluid reaction reversed to normal. There was improvement in the condition of the spinal fluid in 32 percent and in 16 percent a reversal of the blood Kolmer reaction to negative. The authors point out that the 12 percent of complete remissions approximates the majority of estimated spontaneous remissions in cases of general paresis (from 4 to 21 percent, average of 11 percent from 17 reports in the literature). The patients who were given the greatest amount of treatment also responded best serologically. Among the group with asymptomatic general paresis 15 patients, though treated intensively, maintained persistently positive blood and spinal fluid serologic tests, which suggested incipient parenchymatous degeneration. In 1 case there was complete reversal of the spinal fluid reaction to negative and 9 patients were improved. Fourteen patients with tabes dorsalis were treated with discouraging results. One patient with gastric crises, who had been reported by Stokes and Wilhelm as having relief of symptoms for 10 months following the first course of tryparsamide, later had recurrences of symptoms but these were milder than before tryparsamide was administered. Among the group of 6 children with congenital neurosyphilis (5 paresis and 1 tabes with gastric crises) 2 were slightly improved symptomatically and 2 improved serologically. The authors found that the use of tryparsamide in alternation with intraspinal medication every 2 weeks according to the Swift-Ellis technic (Ogilvie modification) did not give as good results as tryparsamide alone. Tryparsamide together with spinal drainage produced no better results than when the drug was used alone. The patients, in

e group which showed reversal of the spinal fluid reactions to normal, were given an average of 34 injections before the serologic reversal was noted, whereas the patients in the group which had the maximal clinical improvement were given an average of slightly less than 20 injections. There were 2 paretics and 5 patients with meningovascular neurosyphilis who relapsed when treatment with tryparsamide was stopped. Among the entire group of 113 there were 14 patients who had relapse of the spinal fluid reaction. In 7 cases of the whole series there was complete reversal of the spinal fluid findings to normal but no associated clinical improvement. The authors conclude that tryparsamide is of value in the treatment of general paresis but that it does not seem to offer as much encouragement as the treatment with malaria.

Schwab and Cady (130, 131) reported that among 230 patients with neurosyphilis who were treated with tryparsamide in conjunction with various other arsenicals and mercury, 80 percent of the meningovascular, about 56 percent of the tabetics, and about 68 percent of the paretics were "arrested in their downward course or were restored to varying degrees of economic usefulness". No details in regard to these patients were presented.

Wolfsohn and Leiva (170) combined tryparsamide treatment with spinal drainage and intravenous injection of a 0 percent sodium chloride solution. In 16 (76 percent) of 21 patients with general paresis who were so treated clinical improvement occurred, and 10 (47.6 percent) returned to work. Ten cases of tabes improved clinically. The most important symptoms that were benefited were lancinating pains, urinary incontinence, incoordination of the legs, and trophic ulceration. Serologic improvement was most marked among the tabetic patients, among whom the reactions changed to negative after 8 treatments in 6 cases.

Others, including O'Leary and Becker (106) and Berg (4), did not observe

that spinal drainage increased the number of good results obtained with tryparsamide.

Kirby and Hinsie (71) reported their observations in the treatment of 69 patients (16 males and 53 females) with general paresis which extended over a period of 2 years and 10 months. For the whole group there were 30 percent of remissions; 22 percent improved, 20 percent were unimproved, and 28 percent died. The authors again reviewed this group of patients 3¼ years after tryparsamide treatment was begun (73). At this time there were 28 percent of remissions; 26 percent were improved, 12 percent were unimproved, and 34 percent were dead. The best results were obtained in young patients who had had symptoms for only a short period of time and in patients with the manic or expansive type of general paresis. There was no agreement between clinical and serologic results.

Fong (42) treated 48 cases of neurosyphilis with tryparsamide. Some of the patients received mercury or bismuth as well. This series included 44 patients with general paresis, 1 with taboparesis, and 3 with cerebrospinal syphilis. He obtained a total of 63.5 percent of remissions (27 percent of which were classified as very good remissions and 36.5 percent as partial remissions), 22 percent were unimproved, and 12.5 percent died. The patients who responded were the agitated and expansive paretics. Neurologically only slight changes were noted following treatment. Speech defect became less evident in some cases and in some the tremors were less marked. There was no definite correlation between clinical and serologic response to tryparsamide. The blood Wassermann was rendered negative in only 50 percent and the spinal fluid Wassermann in less than 40 percent of the cases that were treated for more than 4 years. The cell count and globulin content responded much more quickly than any other element of the fluid. The colloidal gold curve was reduced in the majority of instances but in none of the cases

was there a complete reversal to negative. There was no correlation between the amount of drug administered and the degree of clinical and serologic improvement. Some patients who received only 2 courses of treatment responded as well in some instances and even better than others who had 6 or more courses of treatment. This is probably accounted for by the fact that those who responded best were in the incipient stage of the disease, although in some cases there may be a peculiar individual adaptation to or affinity for this drug.

Solomon and Epstein (147) reported on 81 patients with general paresis who received more than 10 injections of tryparsamide each. These patients were all in a rather early stage of the disease. Treatment resulted in arrest of the disease in 42 percent of cases. In 30 percent the condition remained stationary and in 28 percent there was no improvement. The spinal fluid was reduced to normal in 37.5 percent, was markedly improved in 16.3 percent, was moderately improved in 10 percent and was unimproved in 36.2 percent of cases. The authors noticed that if clinical arrest is to be obtained it will generally occur with 40 to 50 injections. There was no complete parallelism between the clinical results and the spinal fluid findings. Nevertheless, the authors state, significant information is obtained from following the course of the response of the spinal fluid to treatment because a completely normal spinal fluid is a good indication of the arrest of the activity of the disease. None of the patients who were unimproved had a normal spinal fluid. About 80 percent of the arrested cases had a completely normal or nearly normal spinal fluid. The period from the beginning of treatment to the time a normal spinal fluid was obtained varied from less than 1 year to 9 years. There was no significant difference between patients receiving tryparsamide alone and combined with other therapy, except fever.

Hassin and Bassoe (52) presented a detailed and interesting study of 1 patient with general paresis who in spite of intensive Swift-Ellis treatment followed by 33 injections of tryparsamide became progressively worse and died. He had remissions after both Swift-Ellis and tryparsamide therapy but these were of short duration. The blood Wassermann reaction and the spinal fluid findings improved greatly under treatment and were completely negative before the patient died. Post-mortem examination of the brain of this patient showed the inflammatory mesodermal phenomena to be milder than usual in general paresis. Spirochetes were found in the left frontal lobe. The authors concluded that cure of general paresis with modern methods (tryparsamide and malaria) cannot be expected.

Smith (140) treated 9 patients who had acute syphilitic meningitis with tryparsamide. In 5 of these the meningitis developed within or shortly after the time of appearance of the secondary skin lesions, in 4 it occurred in the latent stage. In all of these patients there was a history of head trauma preceding the onset of symptoms. On treatment there was a decrease in the cell count but no change in the Wassermann reaction, colloidal gold curve, or globulin reactions. The symptoms of headache and photophobia were relieved after a few days of treatment.

Menzies (91) reported that tryparsamide can be used as a provocative test in suspected cases of neurosyphilis which have negative spinal fluid reactions. He observed 5 cases in which a provocative dose of tryparsamide rendered the spinal fluid Wassermann positive and 1 case in which the colloidal gold curve also became positive.

The use of tryparsamide for the treatment of neurosyphilis has been met with considerable skepticism in Europe except in Great Britain. The few reports of its use are for the most part based on the results of treatment of a small number

f cases with only a few injections of the drug.

Guillain and Girot (50) treated 3 patients with general paresis and 1 with meningovascular neurosyphilis by means of a course of 8 injections of tryparsamide (3 gm.) and 9 injections of mercury salicylate. The patients with general paresis received only 1 such course, the patient with meningovascular neurosyphilis, 2 courses. A favorable effect was noted in the latter case but there was no effect in the 3 cases of general paresis. Decreased spinal fluid globulin and cell count were the only changes noted. The authors believe that the good result obtained in this one case could have been obtained with the usual treatment as well.

Claude and Targowla (22) reported on the treatment of 10 patients with general paresis by means of tryparsamide. Three of these patients showed some degree of clinical improvement and in 1 of them the spinal fluid also improved except for the Wassermann reaction. In 2 others there was some serologic improvement without clinical improvement. These authors decided that tryparsamide is an ineffective drug, that there is no special indication for its use, but that it is of enough tentative interest to incite further study.

Sicard and Haguénau (135) gave four courses of 21 to 24 injections of 3 gm. each of tryparsamide to 20 patients with general paresis. The courses were repeated after a rest period of 6 weeks so that each patient received about 70 gm. of tryparsamide in 1 year. The patients were followed for 4 years. Two patients died, 1 disappeared after 2 years at which time he was apparently improved, 2 remained stationary. There were 4 remissions (20 percent) in which the serologic reactions also became negative. The authors, however, attributed 2 of these remissions to previous treatment with neoarsphenamine and sulfarsphenamine. Seven improved clinically but not serologically and 4 were unimproved.

Koopman's (74) report, which appears

to be the only study of the effect of tryparsamide in the treatment of neurosyphilis in the German literature, deals with 4 cases of tabes and 3 of cerebrospinal syphilis. A course of 6 injections of 2.5 to 3 gm. each was given to each patient. Aside from relief of headache, lancinating pains, and gastric crises in tabes, no beneficial effects were observed. On the basis of these meager results the author concludes that tryparsamide is not superior to neoarsphenamine or mercury but he suggests that it be given further trial.

Hendriksen (55) states, in discussing the malaria treatment of general paresis, that to his knowledge tryparsamide has not been used in Denmark but that it should be given a trial.

Stürup (158) in his discussion of tryparsamide with reference to the literature states that the Continental skepticism concerning the results with tryparsamide is not justified, although he feels that the results reported are not conclusive. Because so many good clinical results have been reported in the literature, he believes that tryparsamide should be used to supplement malaria treatment. He states that he has used the drug in 20 cases with no untoward effect and has obtained several good clinical remissions.

Cabrera (16) reported marked improvement, both clinical and serologic, in 6 cases of neurosyphilis treated with intraspinal tryparsamide (Swift-Ellis, Ogilvie modification).

In surveying the results obtained with tryparsamide in early general paresis by various authors (Lorenz, Loevenhart, Bleckwenn and Hodges; Lorenz, Loevenhart, Reitz and Eck; Stokes and Wilhelm; Crawford, O'Leary and Becker; Silverston; Keith and Le Marquand; Solomon and Epstein) it is found that from 12 to approximately 70 percent of remissions have been obtained, with an average percentage of 49.7 for this stage of the disease. Advanced general paresis was treated by a much larger number of investigators (Lorenz, Loeven-

hart, Bleckwenn and Hodges; Ebaugh and Dixon; Wile and Wieder; Stokes and Wilhelm; Kennedy and Davis; Reed and Paskind; Crawford; Bluemel and Greig; Smith; Neymann and Singleton; Brown and Martin; Silverston; Kirby and Hinsey; Campbell; Gibbs and Reichenbach; Pijper and Russell; Davie; Stevenson; Ruhberg; Jaenike and Forman; Branche; Kibler; Cormia; Dreyer; and Tennent). The number of remissions obtained varies between 0.0 and 80 percent, the average for this group being 22.5 percent. In taboparesis (Lorenz, Loevenhart, Bleckwenn and Hodges; Lorenz, Loevenhart, Reitz and Eck; Wile and Wieder; Neymann and Singleton) the results also vary between 0.0 and 80 percent with an average figure of 33.5 percent.

TABLE 2.—*Clinical results obtained with tryparsamide in 253 patients with early general paresis (reported in the literature from 1923-35)*

Year studies reported	Number of patients	Average number of injections, tryparsamide	Clinical remission	Improved	No change or worse
			Percent	Percent	Percent
1923-----	12	16	50.0		
1924-----	84	35	41.0	42.0	17.0
1925-----	37	20	59.0	18.9	22.1
1926-----	33	25	56.0	33.0	11.0
1929-----	6	21	50.0	50.0	
1935-----	81	10	42.0	30.0	28.0

TABLE 3.—*Clinical results obtained with tryparsamide in 726 patients with advanced general paresis (reported in the literature from 1923-34)*

Year studies reported	Number of patients	Average number of injections, tryparsamide	Clinical remission	Improved	No change or worse
			Percent	Percent	Percent
1923-----	42	16	50.0		
1924-----	52	20	28.8		
1925-----	179	16	5.8	29.2	65.0
1926-----	240	33	15.8	24.0	60.1
1927-----	48	8	29.2	41.6	29.2
1928-----	100	35	5.0	38.0	57.0
1931-----	28	75	45.5	40.5	13.9
1934-----	37	58		63.0	

TABLE 4.—*Clinical results obtained with tryparsamide in 43 patients with taboparesis (reported in the literature from 1923-26)*

Year studies reported	Number of patients	Average number of injections, tryparsamide	Clinical remission	Improved	No change or worse
			Percent	Percent	Percent
1923-----	5	16	80.0	20.0	
1924-----	14	35	21.0	50.0	29.0
1925-----	12	10		16.7	
1926-----	12	28	33.0	17.0	50.0

The results in tabes are not as good as in other types of neurosyphilis, very few clinical remissions having been reported. From 20 to 75 percent of cases were improved by tryparsamide therapy, with an average figure of 43.8 percent of improvement (Lorenz, Loevenhart, Bleckwenn and Hodges; Lorenz, Loevenhart, Reitz and Eck; Wile and Wieder; Stokes and Wilhelm; Kennedy and Davis; O'Leary and Becker; Neymann and Singleton; Pijper and Russell; Ruhberg; Keith and LeMarquand; Lichtenstein; and Cormia).

TABLE 5.—*Clinical results obtained with tryparsamide in 165 patients with tabes dorsalis (reported in the literature from 1923-34)*

Year studies reported	Number of patients	Average number of injections, tryparsamide	Clinical remission	Improved	No change or worse
			Percent	Percent	Percent
1923-----	5	16	80.0	20.0	
1924-----	29	35		34.0	65.0
1925-----	35	15	29.9	50.3	19.8
1926-----	22	24		36.7	63.3
1927-----	3	9		33.3	66.7
1929-----	24	21		75.0	25.0
1931-----	41	18		51.2	48.8
1934-----	6	58		50.0	50.0

In meningovascular syphilis (Lorenz, Loevenhart, Bleckwenn and Hodges; Moore, Robinson and Keidel; Kennedy and Davis; Branche; Lichtenstein) an average of 44.0 percent of clinical remissions has been reported in the literature.

TABLE 6.—*Clinical results obtained with tryparsamide in 54 patients with meningovascular syphilis (reported in the literature from 1923–31)*

Year studies reported	Number of patients	Average number of injections, tryparsamide	Clinical remission	Improved	No change or worse
			Percent	Percent	Percent
23-----	10	16	90.0	10.0	-----
24-----	10	12	90.0	10.0	-----
25-----	9	-----	-----	77.8	22.2
31-----	10	50	40.0	60.0	-----
31-----	15	27	-----	80.0	20.0

A number of authors have reported on the treatment of neurosyphilis (not assified) (Cocke; Hyder; Burkes; Holmes; Zellin; Foster; Kahn; Menzies; Junker; Skoog; Smith (139); Schelm (125, 126); Berg; Parsons; Hindman; Blair; Kirby and Bunker; Viner; Hecht; Dawson) with considerable variation in the results obtained.

In regard to the effect of tryparsamide in the blood and cerebrospinal fluid all authors are agreed that clinical and serologic improvement are not parallel. Marked clinical improvement may occur without much change in the blood and cerebrospinal fluid findings. The first and most constant changes to occur as a result of treatment with tryparsamide are reductions in the cell count and globulin content of the spinal fluid. The spinal fluid Wassermann and the colloidal gold curve change much more slowly and often only after 100 to 50 injections of the drug have been given. The blood Wassermann tends to be reduced by tryparsamide treatment, but the results obtained show great variation. In summarizing the results obtained in regard to the serologic findings by those authors who have reported them (Lorenz, Loevenhart, Bleckwenn and Hodges; Moore, Robinson and Keibel; Stokes and Wilhelm; Lorenz, Loevenhart, Reitz and Eck; Ebaugh and Dixon; Solomon and Viets; Wile and Wieder; Kennedy and Davis; Reed and Paskind; Crawford; Cocke; Hyder;

O'Leary and Becker; Neymann and Singleton; Davie; Brown and Martin; Silverston; Kirby and Hinsie; Schelm; Jacnik and Forman; Berg; Holmes; Zellin) the following average percentages are obtained in neurosyphilis: The blood Wassermann reaction became negative in 32 percent and was reduced in 21 percent. The cell count of the spinal fluid became normal in 45 percent and was reduced in 21 percent. The globulin of the cerebrospinal fluid became normal in 23 percent and was reduced in 29 percent. The spinal fluid Wassermann reaction was rendered negative in 20 percent and was reduced in 28 percent. The colloidal gold curve of the spinal fluid became negative in 16 percent and was reduced in 35 percent of cases.

SUMMARY

Practically all authors are agreed that in the treatment of neurosyphilis with tryparsamide clinical and serologic improvement are not always concomitant, that reduction in the cell count and globulin of the spinal fluid are as a rule the first serologic changes noted and that the spinal fluid Wassermann and the colloidal gold curve are the most resistant to treatment. When tryparsamide first came into use, beneficial results were expected to occur with comparatively few injections, many authors giving as total treatment between 8 and 20 injections of the drug. As experience grew, it was seen that often more than 50 injections of the drug were necessary to produce the desired changes. A good clinical result with persistently positive serologic reactions was not the desired aim of treatment because of the danger of relapse. Moderate safety for the patient's future was attained only when the spinal fluid was reduced to normal. The ultimate aim of treatment was therefore a normal spinal fluid. It was often observed that this could be attained if the patient was given 50 to 100 or even more injections of tryparsamide, 2 to 3 or even more years of treatment

being required (145, 106, 98, 157). At the same time, it has been noted that the majority of patients in whom improvement finally occurred usually responded to 40 or 50 injections of tryparsamide (149). There are some patients who do not respond even to long continued treatment with tryparsamide and in these a variety of treatment may produce the desired result, as for example Solomon and Epstein's (150) series of 17 patients with general paresis who did not respond to a long course of tryparsamide but finally became clinically and serologically negative after malarial treatment. Clinical and serologic relapse has also to be kept in mind. Relapse in the spinal fluid reactions was noticed by O'Leary and Becker (106) among a group of 113 patients in 12 percent and clinical relapse in 6 percent of cases (2 cases of general paresis and 5 of meningovascular neurosyphilis). Cormia (26) reported 5 cases (11 percent) of a group of 44 who showed relapse (2 early neurosyphilis, 2 early general paresis and 1 advanced general paresis). When tryparsamide first came into use it was suggested that mercury be used concomitantly, and that, in general, has been the accepted form of treatment (mercury or bismuth intramuscularly) although as good results have been obtained with the use of tryparsamide alone. Tryparsamide has been given continuously but as a rule it is at the present time administered in courses of 12 to 16 injections separated by rest periods of 1 month or longer. Stokes (157) states that it has not been definitely settled whether tryparsamide should be used continuously or in courses and that either technic may be accepted as satisfactory.

The results obtained in general paresis, taboparesis, and tabes depend largely on the stage of the disease process. Very good results have been reported by many authors in early general paresis. The duration of the disease and the age of the patient are important factors. It has been noted that the younger patient who is treated soon after the onset of

symptoms benefits most from treatment. In the late cases irreparable damage has been done which no form of therapy can be expected to affect. Many authors report more favorable results in the expansive and manic-depressive types of general paresis. Solomon and Epstein (149) state that the best method of treating patients with general paresis cannot be determined at the present time. In their series various other types of treatment were given in addition to malarial therapy in a large percentage of cases. This consisted of injections of drugs, particularly of tryparsamide and arsphenamine, bismuth, mercury, and the iodides and of fever induced by the virus of rat bite fever, by injections of typhoid vaccine, and by diathermy. They believe that a combination of other methods with malarial therapy gives more satisfactory results than treatment with malaria alone.

The results in taboparesis and tabes are more difficult to evaluate. Many of the reports of tryparsamide therapy are very favorable but it is to be remembered that symptoms which apparently disappear on treatment may recur at a later period so that when patients are observed over a long period of time the final results obtained are not as good as the first impressions. O'Leary and Becker (106) who reviewed Stokes and Wilhelm's (156) series of patients stated that the results in 14 cases of tabes were discouraging. Practically no effect of tryparsamide on ataxia has been observed. Some authors have reported improvement of gastric crises, root pains, or both—Lorenz, Loevenhart, Reitz and Eck (84), 34 percent; Moore, Robinson and Lyman (96), 50 percent; Stokes and Wilhelm (156), several cases; Kennedy and Davis (67), 46 percent; Wolfsohn and Leiva (170), 10 cases; Ruhberg (124), 1 case; Pijper and Russell (114), 1 case; Koopman (74), 4 cases. Solomon and Epstein (145) state that on the whole the results with tryparsamide in tabes are good but they believe intraspinal therapy with the Swift-Ellis

method to be a better type of treatment. They advise preceding the malarial treatment of tabes with tryparsamide.

In congenital neurosyphilis Smith (139) noted marked improvement in 1 out of 3 cases treated with tryparsamide. Stokes and Wilhelm (156) observed 20 percent clinical improvements in 6 cases after 1 course of tryparsamide. O'Leary and Becker (106), in reviewing these 6 cases find that 2 continued to improve clinically and 2 others improved serologically.

Hopkins (58) reviewed the results of various forms of treatment in a group of patients with neurosyphilis of which number 200 died while under observation and 480 were observed for more than 2 years. He found that in late neurosyphilis routine antisyphilitic treatment was much inferior to treatment with arsphenamized serum given subdurally, to tryparsamide, and to malaria. The serum thus administered gave the best results but tryparsamide gave almost as good results. In general paresis and taboparesis malaria was preeminently the treatment of choice. In tabes the best results were obtained with malaria although the results with tryparsamide were almost as good.

Stokes (157) and Moore (98) are essentially in agreement as to the treatment procedure which should be followed in neurosyphilis. Their plan is briefly outlined here for the purpose of defining the place which tryparsamide occupies in the present-day treatment of neurosyphilis: In general paresis and taboparesis, fever therapy, especially malarial therapy, is the method of choice. It should be followed by a short course of neoarsphenamine (Moore) and then by 12 to 16 injections of 3.0 gm. each of tryparsamide. Following tryparsamide 8 to 12 injections of bismuth are given before another course of tryparsamide is started. The purpose of drug therapy following malaria is to increase the probability of complete remission, to prevent parietic relapse, and to prevent the progress of syphilis in other parts of

the body. Moore points out the differences in the spinal fluid changes observed following tryparsamide treatment as compared with those following malarial therapy. Whereas, after tryparsamide, changes are seen early, it may require 18 months before changes occur following malaria, and once they begin they may continue for several years.

In other types of neurosyphilis routine treatment with arsphenamine and heavy metals should first be given for at least 6 months before resorting to tryparsamide. Moore suggests a course of 12 weekly injections of 3.0 gm. each of tryparsamide. Stokes—also Reese (119) and Lees (77)—advises that a small initial dose be given because of the danger of a Herxheimer reaction. If there is no satisfactory response to tryparsamide after 1 year of treatment, fever therapy should be given. Tryparsamide is the treatment of choice in cases where malaria is indicated but cannot be used because of cardiovascular disease, active tuberculosis, old age, debility, obesity, diabetes.

Tabes presents a more complicated problem because of its varied manifestations and their different individual response to various forms of treatment. As a rule at least 6 months treatment with arsphenamine and heavy metals should be given. This is followed by treatment with tryparsamide and heavy metals for 1 year. Since primary optic atrophy is made definitely worse by tryparsamide in the great majority of cases, the method of choice in the treatment of optic atrophy is subdural treatment or malaria. This has also been found to be the most effective treatment for intractable lightning pains, for ataxia, and to produce serologic reversal.

Tryparsamide and malaria are both used in the treatment of congenital neurosyphilis. The results of any form of treatment are generally poor, probably because of the insidious onset of the disease. As a rule, the child with tabes or paresis is old enough to report accurately upon any symptoms produced by

tryparsamide. If the child is not able to do this, the use of tryparsamide is contraindicated.

Tryparsamide should not be given to pregnant women because of the possible danger to the optic nerves of the child in utero and because during pregnancy it is the child rather than the mother who should have the benefit of treatment. For the child's protection a more powerful spirocheticidal drug is indicated.

The only serious contraindication to the use of tryparsamide in cases where it is otherwise indicated, as outlined above, is involvement of the optic nerves which may be present at the time tryparsamide treatment is being considered or which develops as a result of treatment (constriction of the visual fields, decreased vision). According to the reports in the literature—Mayer and Smith (87), Bluemel and Greig (6), Neymann and Singleton (104), Muncy (101), Cady and Alvis (17), Tennent (160), Cormia (26)—a small total number of cases with primary optic atrophy has been treated with tryparsamide without apparent ill effect. However, with the exception of Mayer (who reports improvement in vision produced by tryparsamide in cases with optic atrophy, chiefly an increase in visual acuity), Kahn (64) (2 cases with early primary optic atrophy were improved), and Gerbaux (47) (1 patient's vision seemed improved) there is general agreement that tryparsamide has no beneficial effect on primary optic atrophy. That it has a definitely harmful effect in the majority of cases of optic atrophy is well demonstrated by the amount of permanent damage to the optic nerve observed in these cases, namely 22.7 percent as compared with 2.9 percent in cases where there was no involvement of the optic nerve prior to treatment. (See table 1).

It may be said that with the exception of optic nerve involvement the danger to vision from tryparsamide treatment is not serious, provided each patient receives careful and conscientious ophthalmologic control before and during tryparsamide treatment. This should in-

clude a careful preliminary examination of the fundi and determination of the visual fields and visual acuity. The eyes should be examined at frequent intervals after each of the first 10 injections (especially visual fields and vision) since damage to the optic nerve almost always takes place between the first and tenth injections. Stokes (see Lazar, 76) advises examination on the third day after each of the first 10 injections. Fine and Barkan (41) followed the plan of examining fields, fundi, and vision before the first, third, fifth, and tenth injections and after each tenth injection thereafter. At the time of examination and before each injection of the drug the patient should be carefully questioned in regard to symptoms of glare or dazzling or blurring of vision or the sensation of tremor or waves in the air. If these symptoms are present the eyes should be examined. If no objective changes are found, the drug may be administered again after several weeks. If objective findings occur, tryparsamide should be permanently discontinued. Stokes, Moore, Fine and Barkan, Sloan and Woods, Cormia, and Cady and Alvis have continued its use, in cases where it was otherwise strongly indicated, in spite of slight objective changes but not when these were marked. There is obviously some risk in this procedure and it is questionable if it is justified except in very special cases.

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PUBLIC HEALTH ADMINISTRATION

The Oklahoma prenatal examination law.

G. F. Mathews. *J. Oklahoma M. A.*, McAlester. Aug. 1939, 32: 305.

The prenatal examination law prepared by the American Social Hygiene Association under the direction of Bascom Johnson was introduced in the last session of the Oklahoma State legislature, amended, and passed. The State-wide interest and support of the medical societies did much to assure the passage of this bill. The bill requires that physicians or other persons attending a pregnant woman during gestation shall at her request or with her consent have a test for syphilis made on a sample of the woman's blood. A statement must be made on the birth certificate showing that the test was made, or the reason for its omission. In no case shall the result of the test be stated on the birth certificate. The complete text of the law is given.

Venereal diseases. Lancet, London.
July 22, 1939, 2: 212.

This is a review of the discussions at the ninth Imperial Social Hygiene Congress which recently met in London.

Harrison stated that the number of cases of syphilis treated for the first time at the venereal disease treatment centers in England and Wales had fallen from 42,800 in 1920 to 18,034 in 1938; and the number of infections of less than one year's duration (5,238 in 1938) had fallen by 42 percent since 1931. The infant mortality from syphilis declined from 2.03 deaths per 1,000 live births in 1917 to about 0.20 in 1938. The number of cases of congenital syphilis in the age-group 5 to 15 years declined about 39 percent during the period from 1931 to 1938. There was no decrease in the number of patients over 15 years of age. Harrison stated that it was necessary to redouble efforts to get women under treatment in order to reduce the incidence of syphilis and the late effects in future years. He warned against accepting blindly the first positive Wassermann reaction in pregnant women. Although routine testing is valuable in the prevention of congenital syphilis it may be harmful if used as more than a pointer. Since it seems that the arsphenamines and mercury (unlike bismuth) fail to reach the fetus in effective amounts until the later part of pregnancy, the practice of intensifying arsenical treatment while excluding bismuth, is probably ineffective.

Batchelor stated that of 15,763 blood examinations at the Royal Maternity Hospital and the Elsie Inglis Memorial Maternity Hospital made between Nov. 1, 1934 and Oct. 31, 1938 the percentage of positive results was 0.7 and 3.3 respectively. He stated that people still accepted too readily the degrading and depressing influences resulting from venereal diseases. He said that in his experience the nurse-almoner returned over 90 percent of the defaulters. The relapse-rate in a group of 1,102 patients receiving antisyphilitic treatment at the Edinburg

clinic was 0.9 percent in males (average of 3.6 unit courses) and 3.7 percent in females (average of 3 unit courses). Of 413 notifications of ophthalmia only 5 percent were gonococcal.

Fairfield reported that among more than 13,000 pregnant women attending London County Council clinics during 1935 the percentage who had positive Wassermann and Kahn reactions was only 0.83, and a similar low figure was obtained in 1936.

Prebble described the methods used for assessing the incidence of venereal diseases in the United States. A survey in Toronto (1937) revealed a total incidence of venereal diseases of 9.59 (syphilis 5.64, gonorrhea 3.95) per 1,000 persons. Of the total number, 57 percent were men and 43 percent were women. Compared with the surveys of 1929 and 1931, the number of early cases had decreased 50 percent and late cases had increased by more than 50 percent.

Combating venereal diseases in the U. S. S. R. S. M. Danyushevsky. Am. J. Syph., Gonorr. & Ven. Dis., St. Louis, July 1939, 23: 498.

The People's Commissariats of Health in the Soviet Union republics as well as all local health departments in large cities have special examining boards which supervise the work of institutions for venereal diseases, direct the branch clinics, train medical personnel, and keep records.

Intentional infection with venereal diseases is punishable by 3 years' imprisonment in reformatory labor institutions. The law provides for compulsory treatment of those patients who refuse to undergo treatment voluntarily.

In the Soviet Union there are 2,225 independent institutions and departments for the treatment of venereal diseases at out-patient clinics and general polyclinics, and 10,557 hospital beds for skin and venereal disease patients. Research institutes have been established in almost all the Soviet Union republics to study the most effective methods of

preventing, treating, and combating these diseases. There are about 5,000 doctors, specially trained in venereal diseases, who regularly attend postgraduate courses at state expense in research institutes, special postgraduate medical institutes, or skin and venereal disease clinics at medical colleges.

Sources of infection are investigated by special nurses, and contacts found to be infected are treated. Venereal disease institutions of Moscow and Leningrad have been able to discover and bring to treatment 60 to 70 percent of all persons responsible for spreading the infections.

In 1926 only 35 percent of the patients with syphilis were treated in the primary stage of the disease; in 1935 the percentage reached 70. Of the cases of men registered in 1926 as having gonorrhea, 25 percent had the disease in chronic forms; in 1935 only 1.7 percent of men with gonorrhea had the disease in a chronic form, and the incidence among men had declined to 42.5 per 10,000.

The Soviet Union has 4,000 women and children's consultation clinics in urban centers and 1,638 such clinics in villages. The number of children with syphilis was 15 times greater in 1926 than in 1937. A similar decline is noted among children with gonorrhea. While the birth rate has doubled, the number of infants with congenital syphilis has decreased.

Soviet medicine has achieved considerable success in mastering new methods of treating cases of venereal diseases and now has its own salvarsan preparations: (1) Novarsenol, Soviet neosalvarsan; (2) myarsenol, Soviet myosalvarsan for internal injections; and (3) osarsol, Soviet stovarsol, given by mouth in lozenges. Osarsol can be recommended for treatment of syphilis of the internal organs, the nervous system, and in the final course of treating secondary syphilis. Myarsenol, for intramuscular injection, is prepared by an original electrolytic method, making it pure and free from poisonous admixtures contain-

ing sulfur. Three preparations of organic bismuth for treating syphilis—bismutogvi, bioquinol, and bismoverol—have also been synthesized. Satisfactory therapeutic results have been reported from the treatment of gonorrhea with Soviet white streptocide (para-amino-phenyl-sulfamid).

During the past 15 years, more than 600 venereal disease expeditions and small groups of venereologists have been sent throughout the national republics to assist the local health departments. These traveling campaigners have examined 2,446,000 persons.

A table is presented showing the decline in the incidence of venereal diseases in the Soviet Union from 1913 to 1935. In cities the incidence of cases of first stage syphilis decreased to one-twelfth that of 1913; second-stage syphilis cases decreased to one-seventeenth the figure for 1913; and third-stage cases dwindled to one-tenth the incidence for 1913. The incidence of gonorrhea dwindled to one-third the figure for 1913. Soft chancre seems to have been completely liquidated. This is a direct result of abolishing prostitution.

After a study of data collected from 110,000 post-mortem examinations, Davidovsky reports that the number of persons who died in the U. S. S. R. as a result of syphilis dropped from 8.8 percent of the total number of deaths in 1928 to 1.6 percent in 1932. The data of autopsies during subsequent years, while not yet worked out, indicate a further reduction of this percentage.

LABORATORY RESEARCH

The effect of sulphonamides on blood-serum. G. Allan Scott and O. Meerapfel. *Lancet*, London. July 29, 1939, 2: 244.

Two cases with bacteremia are described in which treatment with a sul-

sulfonamide over a long period and in large total doses (423 grains of uleron in one case and 748 grains of sulfanilamide in the other) was followed by an alteration in the blood serum which precluded the finding of a suitable donor for blood transfusion.

Normal serum treated in vitro with sulfanilamide for 4 days or more agglutinated the red blood cells of donors of the corresponding blood group and the cells of universal donors.

When these drugs were administered over shorter periods and in smaller doses to 6 other patients such a change in the blood serum did not take place.

The passage of sulfonamides into the glandular secretions of the urogenital system. W. W. Kühnau. *Med. Klin.*, Berlin. June 30, 1939, 35: 883.

The technic of a micromethod for the determination of albucid is described in detail and the findings obtained in 15 patients by the use of this method are reported. Albucid determinations on serum and prostatic secretion (obtained through prostatic massage or ejaculation) were carried out simultaneously. The amount found to be present in the ejaculate was only slightly less than that found in the serum, while the values for prostatic secretion were considerably higher than those for serum. Albucid therefore was present in the glandular secretions of the urogenital system in sufficiently high concentration to be effective. Failure of patients to respond to treatment with albucid cannot therefore be attributed to insufficient concentration of the drug in the lumina of these glands.

Protective antibodies in the serum of human syphilitics. Thomas B. Turner, William L. Flemming and Nancy L. Brayton. (*Proc. Am. Soc. Clin. Investigation.*) *J. Clin. Investigation*, Lancaster. July 1939, 18: 471.

The authors report the results of protection tests made on the serums of 80 persons, 60 of whom had or had had syphilis, and 20 of whom were presumably nonsyphilitic.

One part of a tissue emulsion rich in virulent *T. pallidum* was combined with 9 parts of whole serum, the mixture incubated for 6 hours at 37° C., and inoculated intracutaneously in 6 sites of one area in each of 4 normal rabbits. Serums were tested in groups of 4, one serum of each group being from a presumably nonsyphilitic person. The same lot of spirochete emulsion was employed in all but one group of tests. Protection was manifested by failure of syphilitic lesions to develop at the sites of inoculation or by a prolonged incubation period as compared with the lesions in the control area.

Of 60 serums from persons with syphilis, 53 gave definite evidence of protection; in 4 the results were equivocal, and in 3 there was no evidence of protective antibodies. Of 20 serums from presumably nonsyphilitic persons, 16 showed no evidence of protection, in 2 the results were equivocal, and 2 showed definite protection. Of 11 syphilitics with negative Wassermann tests, the serums of 10 contained protective antibodies.

Development of tolerance to organic arsenicals in laboratory animals. M. L. Kuhs, B. J. Longley and A. L. Tatum. *J. Pharmacol. & Exper. Therap.*, Baltimore. July 1939, 66: 312.

During the investigation of a number of organic arsenical preparations the authors observed that some of the laboratory animals appeared to have developed a tolerance to certain of these compounds. This tolerance was beyond the range of individual variation and, therefore, it seemed of interest to determine whether tolerance could be developed regularly in laboratory animals.

The experiments were begun with an intravenous dose of from 50 to 90 percent of the maximal tolerated dose, and this was increased by 10 to 50 percent, depending on the severity of toxic symptoms. Subsequent injections were usually given at weekly intervals for rats and at intervals of 2 weeks for rabbits and dogs. Thus, from 5 to 8 injections and as many weeks were required for the

development of the tolerance values reported.

The character of the compound used was found to be an important factor governing tolerance development, as was also the dose selected, the interval between injections, and the species of animal. It was found that there was an optimum time interval between injections; if the interval was too short, the animal became more sensitive to the compound.

The experiment showed that a significant tolerance to certain organic arsenicals was developed in rats, rabbits, and dogs. A definite tolerance to inorganic arsenic preparations could not be developed in rats. A cross tolerance between certain organic arsenicals could be developed, but it could not be developed between organic and inorganic arsenic preparations.

The formation of methemoglobin and sulfhemoglobin during sulfanilamide therapy. J. S. Harris and H. O. Michel. (Proc. Am. Soc. for Clin. Investigation, May 1939) J. Clin. Investigation, Lancaster. July 1939, 18: 496.

From 476 patients who were given sulfanilamide 960 blood samples were examined for free sulfanilamide, methemoglobin, and sulfhemoglobin. Spectrophotometric determinations were made in the 277 patients who had methemoglobinemia and in the 37 who had sulfhemoglobinemia.

The percentage of blood samples in which methemoglobin was found was highest in the group that had high sulfanilamide content, and the average methemoglobin was proportional to the sulfanilamide concentration. The presence of methemoglobinemia did not depend on sex, but was more pronounced and frequent in the very young. The methemoglobin concentration tended to diminish with increasing duration of therapy at constant blood sulfanilamide levels up to 8 mg. percent, but at higher sulfanilamide concentrations there was a tendency for the methemoglobin to increase with time.

Sulfhemoglobinemia was more frequent after long courses of sulfanilamide, but

did not bear any relationship to age, sex, or the concentration of sulfanilamide or methemoglobin in the blood.

From these findings it was assumed that an active substance is produced in the course of sulfanilamide metabolism which causes the production of methemoglobin and sulfhemoglobin. The statistics presented are found to agree with the concept that methemoglobinemia depends upon a balance of the following reactions: Formation of the active agent, oxidation of hemoglobin under the influence of the active agent, and reduction of methemoglobin by the body.

Cyanosis caused by sulphonamide compounds. David Campbell and Thomas N. Morgan. Lancet, London. July 15, 1939, 2: 123.

In cyanosis developing during the therapeutic use of 2-p-aminobenzene-sulfonamidopyridine (sulfapyridine) and p-aminobenzenesulfonamide (sulfanilamide), when there is no other obvious cause, careful spectroscopic examination of the blood always demonstrates the presence of either methemoglobin or sulfhemoglobin. When examining the blood spectroscopically for methemoglobin, it is essential that the sample should be laked with only a small volume of water and examined soon after withdrawal. Otherwise the presence of the pigment may not be detected. These precautions are not so essential when determining the presence of sulfhemoglobin.

The authors describe in detail the procedure followed in making their spectroscopic analyses.

In cases treated with sulfanilamide the pigment formed may be either methemoglobin or sulfhemoglobin, but in the authors' experience it has usually been the latter. The pigment formed during treatment with sulfapyridine is practically always methemoglobin.

In methemoglobinemia, methylene blue is effective in causing the rapid disappearance of the cyanosis by converting methemoglobin to hemoglobin. The dye is active when given intravenously, intramuscularly, or by mouth. The

authors report in detail the cases of 4 patients in whom methemoglobinemia quickly disappeared following treatment with methylene blue. It is suggested that the routine employment of methylene blue in conditions requiring prolonged administration of sulfapyridine may be a useful measure in preventing cyanosis. Methylene blue has no effect in preventing or modifying the cyanosis of sulfhemoglobinemia.

Effects of anesthetic drugs upon rats treated with sulfanilamide. John Adriani. *J. Lab. & Clin. Med.*, St. Louis. July 1939, 24: 1066.

Toxic reactions have been reported when patients under sulfanilamide treatment have been given magnesium sulfate or other depressing drugs. The present study was undertaken in order to observe the reactions of animals treated with sulfanilamide and subjected to anesthesia with various drugs in current use. A special strain of white rats was used for the experiments, and they were treated with sulfanilamide (0.5 to 1.0 mg. per gram body-weight daily) for 3 days. These animals and a similar number of untreated controls were given various volatile, gaseous, and nonvolatile anesthetic drugs, and were also subjected to asphyxia and carbon dioxide excess.

Reactions to ether and chloroform, to nitrous oxide and cyclopropane, and to carbon dioxide excess or oxygen want were the same in treated and untreated rats. There was practically no difference in the reaction to tribromethanol (avertin) in the two groups.

Treated rats which were given evipal, pentothal, thioethamyl, amytal, or nembutal reacted unlike the untreated rats. The subanesthetic doses became anesthetic and often lethal, and anesthetic doses were usually lethal. The thio derivatives of barbituric acid were the worst offenders. The treated rats which were allowed 4 days for recovery did not show this reaction. It was also less intense early in sulfanilamide therapy and more intense with increased dosage of the drug.

Adriani believes that the combination of sulfanilamide and barbiturates may be unwise in human therapy.

The effect of sulfhydryl compounds on the antispirochetal action of arsenic, bismuth, and mercury compounds in vitro. Harry Eagle. *J. Pharmacol. & Exper. Therap.*, Baltimore. Aug. 1939, 66: 436.

The finding that arsenoxide, some of the arsphenamines, and numerous bismuth compounds immobilize and kill *T. pallidum* in vitro suggested to Eagle an experimental test of the hypothesis of Voegtlin, Dyer and Leonard that the arsenic may combine with sulfhydryl groups in trypanosomes. Various sulfhydryl compounds were added to mixtures of arsenicals, bismuth, or mercury compounds, a suspension of *T. pallidum* was then added, and the degree and rate of immobilization of the organisms were determined by direct observation.

Eagle found that sulfhydryl compounds (cysteine, glutathione, and thioglycollic acid) added in sufficient excess to arsphenamine, neoarsphenamine, silver arsphenamine, arsenoxide, bismuth, or mercury compounds almost completely abolish their antispirochetal action in vitro. The large excess which is necessary to cause complete inactivation of the arsenicals suggests that the additional compound may be readily hydrolyzed. Thiamin chloride and methionine, which contains a -S- rather than a -SH group, have no inhibitory effect.

The fact that all the antispirochetal agents here tested are rapidly and almost completely inactivated by the addition of sulfhydryl compounds is consistent with the hypothesis that they owe their therapeutic activity to similar combinations with sulfhydryl groups in the spirochete. Moreover, the fact that the three groups of compounds most actively spirocheticidal (arsenic, bismuth, and mercury) all have in common this marked affinity for sulfhydryl compounds is strongly suggestive. Eagle says it need hardly be pointed out that

these data do not constitute positive evidence.

A new method for cleaning and sterilizing Kahn or Wassermann tubes. N. O. Gunderson and C. W. Anderson. J. Lab. & Clin. Med., St. Louis. July 1939, 24: 1085.

The writers describe a method for cleaning tubes which they say results in a uniform and complete cleansing, rinsing, and drying of each tube, with a marked saving in the cost and time required for cleaning operations. Wire cloth of 4-mesh stainless steel No. 304, 18 percent chromium, 8 percent nickel, is used to make a basket 6 inches by 6 inches by 3 inches. Square-foot sections of the cloth are folded into the basket by cutting three-inch triangular sections from each corner of the square. A top is made for the basket from a six-inch square.

Tubes may be transferred directly from the Kahn racks to the basket, packing them uniformly to facilitate rapid rinsing. They are rinsed several times in warm alkaline detergent, then in tap water, and are immersed in chromic acid cleaning solution for a minimum of 4 or 5 hours. They are then given at least two rinses in tap water, rinsed twice in distilled water, and the basket is placed in a drying oven at 120° C. The capacity of this basket is from 140 to 150 tubes, and a basket 6 by 6 by 6 inches could be made if a greater capacity is desired.

The effect of various forms of particulate carbon on the growth of the gonococcus and meningococcus. V. Glass and S. J. Kennett. J. Path. & Bact., London. July 1939, 49:125.

The authors summarized the results of their experiments as follows: The addition of certain preparations of carbon to nutrient agar greatly increases the suitability of this medium for the growth of *N. gonorrhoeae* and *N. meningitidis* and with the former this is particularly evident when incubation is carried out in 1.5 to 5 percent CO₂. The effect is produced by blood charcoal, by blood charcoal and sugar charcoal heated to 1,000°

C. for 1 hour, and by graphite but not by commercial sugar charcoal or Merck medicinal charcoal. The effect is not due to soluble matter contained in the carbon powders or to organic compounds which decompose on exposure to temperature up to 1,000° C. for 1 hour.

To enhance growth, the carbon particles must be present in the medium during incubation of the inoculum; mere exposure of the medium to carbon which is subsequently removed does not confer upon the new growth-promoting property.

Kaolin and red oxide of iron do not improve growth of either gonococci or meningococci, while chalk powder improves that of the meningococcus but not of the gonococcus.

PATHOLOGY

Syphilis and carcinoma of the cervix

M. Sorba. Monatschr. f. Geburtsh. Gynäk., Basel. May 1939, 109:73.

During the period from 1927 to 1935 262 cases of carcinoma of the cervix the uterus were hospitalized on the gynecologic ward of the University Lausanne. A Wassermann and a Vern flocculation test were made on the blood of 240 of these cases. These reactions were positive in 32 cases. In 1 case in which a blood test had not been made syphilitic aortitis was found at autopsy. In 4 seronegative cases a definite history of syphilis and of previous antisyphilitic treatment was obtained. Therefore a total of 37 cases (14.1 percent) of syphilis was found in this group. The incidence might even be higher because in 22 patients of this group no serologic examination for syphilis was made. Among the other patients in the gynecologic and obstetric wards of this hospital the incidence of syphilis was 1.6 percent. Among 89 cases of carcinoma of the genital tract other than the cervix (namely of the uterus, ovary, vagina and vulva) no positive serologic reactions were

ound. Among 347 patients with carcinoma of the skin who were seen in the dermatology clinic, only 5 (1.47 percent) had or had had syphilis. There were no congenital syphilitics among the 37 cases with carcinoma of the cervix and three-fourths of them had never received anti-syphilitic treatment, whereas the other fourth had been inadequately treated. The author points out that the occurrence of falsely positive serologic reactions in cases with carcinoma is extremely rare. Among the 8 patients who had received treatment for syphilis, the time of infection could be ascertained in 6 and was 29, 15, 14, 10, 9, and 5 years. The highest incidence of cancer was in the age groups of 40 to 50 and 50 to 60 years for both syphilitic and nonsyphilitic patients. The degree of extension to the adnexa and the types of carcinoma were the same for both groups, being chiefly epitheliomas. The number of 5-year cures of carcinoma was the same for the syphilitic as for the nonsyphilitic group.

The author advises that in cases having both carcinoma and syphilis the carcinoma be treated first. Both diseases cannot be treated simultaneously because the reactions produced by radium or X-ray can simulate those due to arsenic intolerance.

The author concludes that syphilis may be a factor in the etiology of carcinoma of the cervix. Apparently syphilis predisposes a person to carcinoma, which develops, once it has started, in the same manner as in the nonsyphilitic person. Prophylaxis and treatment of syphilis probably decrease the incidence of cervical carcinoma.

Tuberculosis and syphilis. H. C. G. Seimon. Brit. J. Ven. Dis., London. July 1939, 15: 159.

It is self-evident that a man who has syphilis cannot contract syphilitic primary chancre, and an identical stipulation applies to tuberculosis which explains the extreme rarity of the primary tuberculous "chancre." The tuberculous lesion differs from that in syphilis in sev-

eral particulars; the infiltration is softer and the edges are flat and somewhat overhanging, while the base has a rather granular appearance and tends to bleed more easily.

The histologic differentiation of the tuberculous from the tertiary syphilitic lesions is based on the fact that tubercles due to Koch's bacillus are more frequently multiple, while the gumma is usually a solitary infiltration with a strong tendency to necrose in its center. The author treats of the clinical differentiation of the cutaneous manifestations of the two infections and he discusses these manifestations according to the various regional areas which may be involved. On the scalp, the moth-eaten appearance of the syphilitic secondary stage, with or without roseola, is never seen in the diffuse fall of hair due to tuberculosis. Interesting problems of diagnosis occur on the area including the face, the ears, and nose. Lupus vulgaris is the commonest example of tuberculous infection. Cutaneous gummas can be mistaken for scrofuloderma which is more apt to occur on the neck than on the face. A history of cervical tuberculous adenitis may afford the diagnostic clue in nearly every case of so-called scrofuloderma. When something resembling it occurs for the first time in the adult, a Wassermann test should always antedate any surgical procedure. Tuberculous ulcers of the lips, gums and buccal mucosa are usually painful and have a more eroded and frayed appearance than syphilitic lesions.

Verrucose tuberculid is the commonest tuberculous manifestation of the forearms and hands. When the warty character prevails on palms and soles it is much more likely to be syphilitic than tuberculous. Difficulty may sometimes arise in diagnosis between tuberculids and papular syphilids occurring on the trunk, and it must be remembered that the former may occur in children with a positive Wassermann reaction. The syphilids are usually universal and may be associated with lesions of the mucous membranes. In the anogenital region

the difficulty in diagnosis is not so much the differentiation between tuberculosis and syphilis as between syphilitic and other ulcers and nonulcerative infiltrations. Perianal sinuses are more likely to be tuberculous than syphilitic. A practically diagnostic characteristic of tuberculosis is the tendency to recurrences in scar tissue. Cicatrization in tuberculous cases is more likely to be followed by deformities than in parallel syphilitic involvement.

Pulmonary tuberculosis and syphilis.

R. R. Trail. *Brit. J. Ven. Dis.*, London. July 1939, 15: 171.

Medical opinion is strongly divided in regard to the incidence and extent of pulmonary syphilis. Since the final proof must always be demonstration of the organism in the lesions or their products, and in lung cases such proof is almost always missing, definite diagnosis of pulmonary syphilis cannot be established as it can be in tuberculosis. Radiologists contend that there are no essential characteristics and that diagnosis in such cases rests on elimination of the other possible causes. Even the proof of improvement by treatment is not completely satisfactory, for other conditions, such as amebic diseases, are known to be amenable to certain anti-syphilitic measures. There is, however, a fairly definite radiologic finding in lung films of certain cases of syphilis, and when it is present a positive Wassermann reaction is not unusual. This consists of a marked central fibrosis extending from the hilum outward to the periphery in fan-shaped distribution and nearly always equally marked on both sides. There is danger of missing the presence of pulmonary tuberculosis in syphilitic persons unless full investigation of the bronchitis in the secondary stage is undertaken, and an equal danger of missing the diagnosis of coincident syphilis in persons with pulmonary tuberculosis unless the extent of fibrosis is studied.

Since tuberculosis and syphilis are both comparatively common, it is inevitable that a certain number of patients

will have both conditions. Various authorities show that from 3 percent to 17 percent of all patients with one or the other condition have both conditions. An investigation carried out in England from 1931 to 1934 showed that 1.42 percent of 774 patients with positive sputum had a positive Wassermann reaction confirmed by the patient's history.

It has been almost impossible to come to a definite conclusion as to whether syphilis aggravates tuberculosis and makes it caseous or not; for it would be necessary to know the time at which each of the diseases was contracted. Trail believes that the conclusions of Dujardin and Duprez that secondary syphilis always aggravates tuberculosis while tertiary syphilis exercises a favorable action and produces fibrosis are true. From a study of other figures it would seem that there is no definite predisposition to tuberculosis among syphilitics.

Literature on the interplay of the two diseases is very contradictory. Figures are quoted which seem to prove that syphilis coincident with tuberculosis has a very favorable influence on the type and development of the tuberculosis and that treatment of the syphilis produces a marked improvement in the tuberculous lesion. Observations by the author on 14 cases diagnosed as having both diseases between 1927 and 1934 and followed up to date support these views.

Coexisting tuberculosis and syphilis

Frederick C. Warring, Jr. *Am. Rev. Tuberc.*, New York. Aug. 1939, 40: 175.

During the 10 years following Jan. 1, 1928, routine serologic tests for syphilis were performed on 2,160 patients admitted to the Laurel Heights State Tuberculosis Sanatorium (Connecticut). All of the patients, syphilitic and nonsyphilitic, were treated according to the modern concept of the management of pulmonary tuberculosis. Among the 2,160 admissions there was a diagnosis of syphilis in 87 patients (4.0 percent). Of the white patients 3.2 percent were syph

tic and of the Negro patients, 26.0 percent. There were 22 patients with positive or doubtful reactions who could not be given a final diagnosis of syphilis, and these 11 were repeatedly doubtful reactors. There were 68 cases of latent syphilis and 3 with a history of serologic cure among the cases diagnosed as syphilis.

In studying the behavior of pulmonary tuberculosis in a syphilitic patient Warring found from data of general hospitals and clinics that the incidence of active tuberculosis in syphilitic patients was not greater than in nonsyphilitic patients. His data showed that the extent of tuberculosis was practically the same in the two groups when they were admitted to the sanatorium. He says that he cannot give an explanation for the fact that pulmonary tuberculosis in the syphilitic patient did not respond as favorably to sanatorium treatment as did the disease in the nonsyphilitic. This unfavorable trend appeared to be greater in the syphilitic Negro than in the white patient. It is interesting that tuberculosis in those patients with active syphilis was shown to run a more favorable course than in those with latent syphilis.

The course of syphilis in patients with tuberculosis does not appear to differ from the course of the disease in the non-tuberculous. The question of the influence of antisiphilitic treatment on the course of tuberculosis cannot be answered; patients with an unfavorable tuberculous condition are purposely not given antisiphilitic treatment and this group would show a high death rate and unfavorable results. On the other hand, patients with good prognosis were the ones singled out for antisiphilitic treatment, and their pulmonary disease could be expected to show more favorable courses.

Warring believes that a definite clinical diagnosis of syphilis of the lung is impossible. Its symptomatology may be confused with that of tuberculosis or bronchiectasis or cardiac disease. In the 106 patients that had positive or doubtful

serologic tests when admitted to the sanatorium there was not one that could be diagnosed as having syphilis of the lung.

Observations on 8 cases of general paresis occurring in native Algerian Mus-sulmen. F. Ramee, F. Maril and F. Porot. Bull. Soc. franç. de dermat. et syph., Paris. Apr. 1939, 46: 738.

From the opening, in 1935, of the psychiatric service of the Constantine Hospital, until December 31, 1938, the number of cases of general paresis observed were as follows: Seven out of 108 European men, 5 out of 216 native men, 1 out of 23 Jewish men, 2 out of 115 European women, 3 out of 86 native women, 1 out of 46 Jewish women. Among a total, therefore, of 323 European patients there were 9 cases of general paresis, or 1 out of 36 as compared to 8 cases among the total of 302 natives, or 1 out of 38. The authors conclude that the incidence of general paresis is as high in hospitals for the insane among the natives as among the Europeans. The 8 native cases are described in detail but present no unusual features.

Osteopathies due to bismuth. J. Ra-couchot. Bull. Soc. franç. de dermat. et syph., Paris. Apr. 1939, 46: 728.

The author reports the case of a 36-year-old woman who during the course of treatment for latent syphilis received at least 250 intramuscular injections of bismuth hydroxide (at the rate of about 10 injections per month), for a period of 2½ years. Soon after treatment was stopped dull pains developed in the region of the first dorsal vertebra which radiated to the left scapula. On treatment with nearsphenamine the pain continued. A roentgenogram showed osteoporosis of the first 4 dorsal vertebrae. When bismuth was again administered in order to establish its etiologic significance, the pain was greatly increased. The author believes that the osteoporosis in this case was due to bismuth.

Sulphanilamide in the air: A warning.
F. P. Mackie. Brit. M. J., London.
July 15, 1939, 2: 139.

Sulfanilamide and related compounds, when given in full doses or to patients with an idiosyncrasy toward the drugs, may interfere with the oxygen exchange of the body by the production of methemoglobin or sulfhemoglobin in the circulating blood.

In this letter to the editor, the author reports the case of a pilot who suffered from the symptoms of severe anoxemia as a result of flying at the moderate altitude of about 13,000 feet. It was found that he had been taking full doses of sulfanilamide for a septic tonsillitis just previous to flying. Other such cases have been reported in America and England. A full dose of one of these drugs taken shortly before flying is said to lower an aviator's "ceiling" by about 5,000 feet. Persons intending to fly as passengers, and, more particularly, as members of an aircraft crew should be warned of the danger of taking these drugs within a few days of flying. A few days would probably suffice to insure proper elimination of the drug from the body.

Bacterial endocarditis (acute and subacute) superimposed on syphilitic aortic valvulitis. Albert L. Braunstein and Stuart A. Townsend. (Proc. Am. Soc. for Clin. Investigation, May 1939) J. Clin. Investigation, Lancaster. July 1939, 18: 491.

Though syphilitic aortic valvulitis and vegetative bacterial endocarditis are established as separate entities, the authors have found but 11 proved cases in which these diseases occurred concomitantly.

Autopsy reports revealed 9 cases among 4,936 routine autopsies, and this represents 15.5 percent of all their cases of bacterial endocarditis and 3.37 percent of their cases of syphilitic aortic valvulitis.

An analysis of the authors' 9 cases, as well as the reported cases, revealed that both acute and subacute types of endocarditis are superimposed on syphilitic aortic valves. Clinically, in the subacute

cases the predominating signs and symptoms were those referable to syphilitic aortic insufficiency with myocardial failure. In the acute cases, evidences of septicemia were usually obvious and myocardial failure was quite striking.

From the findings, the authors conclude that with obvious signs of bacterial endocarditis in the presence of syphilitic aortic insufficiency, the bacterial process most likely exists on a valve other than the aortic. However, the presence of bacterial endocarditis of a syphilitic aortic valve may be suspected when, in the presence of aortic insufficiency, there is a gradually progressive anemia and daily intermittent temperature rises which cannot be explained by any other findings.

Psychosis due to sulfanilamide. Robert E. S. Young. Ohio State M. J., Columbus. Aug. 1939, 35: 847.

Toxic effects on the nervous system following sulfanilamide therapy have not been common. Optic neuritis and peripheral neuritis have been reported following sulfanilamide treatment. Peripheral neuritis has been noted following the administration of sulfanilyl-sulfanilamide.

Hogan and McNamara reported a case of psychosis characterized by delirium, delusions, and hallucinations following sulfanilamide treatment. Silver and Elliott listed one case of psychosis.

In this article, Young reports the case of a white man, 37 years of age, who became amnesic after voluntarily taking sulfanilamide. The exact dosage could not be discovered, but the patient probably took 90 to 150 grains daily for at least a week. Although the patient had complete loss of memory for past events, he could name objects and he showed some ability to reason. His pupils were fixed, the Romberg sign was positive, the tendon reflexes were irregular, and there was a bilateral suggestive Babinski sign. He had a mild macular rash on the face.

His employer and members of his family gave a history of progressive mental deterioration over a period of 3 weeks. This deterioration was characterized by

violent fits of temper, melancholia and mental confusion.

He became mentally clear and the neurologic examination was normal 96 hours after he was hospitalized for treatment and observation.

Contribution to the clinical findings and histopathology of juvenile paresis.

F. Tebelis. Ztschr. f. d. ges. Neurol. u. Psychiat., Berlin. Apr. 25, 1939, 166:178.

The author presents a very detailed description of the clinical and anatomic changes in 11 cases of juvenile general paresis. He emphasizes the significance of convulsions in producing anatomic change and differentiates this type of anatomic change from that of parenchymatous degeneration produced by general paresis per se. In 4 cases marked changes were found in the occipital lobes and were correlated with many apoplectic attacks which had been clinically observed in these cases. He confirms the finding by many authors of typically philitic changes in juvenile general paresis. He observed one case in which there was a combination of juvenile paresis and endarteritis of the small blood vessels of the cortex and calls attention to the histologic similarity of these changes and those found in Wilson's disease and in Wernicke's polioencephalitis, suggesting that possibly metabolic disturbances are factors in producing these changes. The difficulties of histologic differential diagnosis between juvenile paresis and many vague encephalitides occurring in childhood are discussed.

Gonococcal endocarditis, with recovery after sulfapyridine. Report of a case. Edward S. Orgain and Mary A. Poston. New England J. Med., Boston. Aug. 3, 1939, 221:167.

The author reports the case of a housewife (aged 24) with bacterial endocarditis, due to the gonococcus and a non-hemolytic anaerobic streptococcus, superimposed upon the pulmonary valve. The

patient recovered following the oral administration of sulfapyridine. Recurrent chills and fever, pulmonary insufficiency, and leukocytosis indicated endocarditis. Five consecutive blood cultures positive for gonococci and nonhemolytic anaerobic streptococci, together with X-ray evidence of pulmonary embolization, were considered diagnostic.

Hospital treatment was begun with high caloric and high vitamin diet, iron, liver, and blood transfusions. On the sixth hospital day, sulfapyridine was started, 0.3 gm. every 6 hours for 2 days, 0.6 gm. every 6 hours for the next 12 days, 0.9 gm. every 6 hours for the next 7 days, and then 5.0 gm. daily for the next 31 days. Blood sulfapyridine determinations varied from 4.0 to 7.3 mg. per 100 cc. at this dosage level. Clinical recovery under treatment was indicated by a general improvement in the patient's condition, the subsidence of fever, regression of the heart lesion, and disappearance of the pulmonary infarct as disclosed by roentgenograms and the repeatedly negative blood cultures. There was an unusually prompt response of the fever to sulfapyridine on the first day of drug therapy, indicating an antipyretic effect of the drug. Of the two organisms involved, the gonococcus was more vulnerable to sulfapyridine treatment since it disappeared from the blood stream first. The only toxic effects of treatment were slight cyanosis and transient nausea on doses of 5 gm. daily. The reappearance of a slight anemia (3,690,000 red cells) near the end of the hospital stay may have been due to prolonged administration (52 days) of the drug.

Coincident with the disappearance of the bacteremia, immune bodies appeared and increased to high titer, and the gonococcal complement fixation test (initially 4+) became negative. This inverse relation of immune bodies to complement fixing antibodies is important. The appearance of the former in high titer and the disappearance of the latter, together with the subsidence of all clinical signs, probably indicate a cure.

DIAGNOSIS

A comparison of the Wassermann and Meinicke (M. K. R. II) tests in the serological diagnosis of syphilis. M. M. Barritt. *Brit. J. Ven. Dis.*, London. July 1939, 15: 183.

The serums for this investigation were obtained from the Seamen's Dispensary and Mill Road Infirmary, Liverpool, and were from cases of registered or clinical syphilis. In the first specimens from 1,000 consecutive cases, the Wassermann reaction (W. R.) was positive in 81 percent and the Meinicke (M. K. R. II) in 93 percent. The tests agreed in 80 percent of the cases. Among cases of untreated syphilis there was agreement in 87 percent and among treated cases in 73 percent. In no stage of syphilis was the W. R. more sensitive than the M. K. R. II. The difference between the tests was greater among treated than among untreated cases, particularly in cases of latent, congenital and neurosyphilis, and in untreated patients this higher sensitivity was very evident with primary and neurosyphilis. This difference in sensitivity was found to be lessened by increasing the concentration of the patient's serum used in the Wassermann test.

For evaluating the nonspecificity of the 2 tests, 1,600 cases of gonorrhea, chancroid or nonvenereal disease were studied, and it was found that 0.25 percent were positive by the W. R. and 1.25 percent by M. K. R. II.

From these findings the author believes that the M. K. R. II is a valuable test to use in parallel with the W. R. for the diagnosis of syphilis. Of equal importance are the ease with which the results can be read, the simplicity of technic, and the saving of time and material in doing the tests.

In an addendum to the above article, A. O. Ross expresses his belief in the value of the M. R. K. II. He says it

seems to be an excellent test for use in connection with the routine W. R. since its nonspecificity is slight and its sensitivity is such that it reveals the case which has not been adequately treated and leads to biologic cure. It is of valuable assistance in the diagnosis of early primary and late syphilis, and especially of neurosyphilis. He is impressed with the diagnostic and directive value of the M. K. R. II in the conduct of treatment.

Evaluation of the pallida reaction.

W. Zündel. *Arch. f. Dermat. u. Syph.*, Berlin. May 27, 1939, 179: 120.

The author considers the pallida reaction as a valuable diagnostic aid if it is used in conjunction with the complement fixation and flocculation reactions but warns against attaching too much significance to it in the individual case. Syphilis should not be diagnosed on the basis of a positive pallida reaction in the presence of otherwise negative serologic and clinical findings. He presents several tables to show the occurrence of falsely positive pallida reactions as based on a comparison with flocculation reactions done simultaneously on the same serums.

The Laughlen rapid test for syphilis. A new technique employing Garrow's agglutinator. A. H. Walters. *Brit. J. Ven. Dis.*, London. July 1939, 15: 228.

A modified technic for the Laughlen test is described which makes use of a known quantity of reagent, a known quantity of serum, an agglutinator revolving 15 times a minute, set reading times, and increased facility for doing numbers of tests. Ten cc. of blood was withdrawn from each of 400 consecutive patients attending the venereal disease clinic at Albert Dock Hospital, and each serum was tested by the Kahn and the Laughlen test (modified technic). Of these 400 cases, 57 were diagnosed clinically as syphilis and 343 as not syphilis. Analysis of the 57 cases showed that the Kahn test was in complete agreement with the Laughlen in all the positive cases, but that the Kahn was very slightly more sensitive than the Laughlen test in

registering weak or doubtful reactions in old cases.

From the analysis of the 343 cases diagnosed as not having syphilis, it appeared that the Laughlen test may give a doubtful reaction in 1.7 percent of such cases compared with 0.6 percent with the Kahn test.

Walters concludes from the results of these tests that the Laughlen rapid test (modified technic) is a very reliable test for syphilis cases that normally give a Kahn three plus or four plus result. Since it is usual to accept with reserve doubtful positive results in the serodiagnosis of syphilis by any test, the Laughlen test (modified technic) may be considered a useful general rapid test for syphilis subject to later confirmation by the Kahn test in all serums giving a doubtful positive result.

The gonococcus complement fixation test in gonococcal infections treated with sulfanilamide. Alfred Cohn. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis. July 1939, 23: 461.

The author reports the results of a serologic analysis (using the gonococcus complement fixation test) of 59 patients with definitely proved gonorrhea who were treated with sulfanilamide. The patients were followed up clinically, bacteriologically, and serologically over an average period of 1 year or more. The bacteriologic diagnosis of gonorrhea was based upon Gram-stained smears and on cultures. The criteria of cure included repeated negative smears and cultures from the urethra, cervix, prostatic and sometimes spermatic secretions, and urethral smears in addition to the absence of symptoms and clinical signs of infection.

The specificity of the gonococcus complement fixation test was not influenced by sulfanilamide therapy which was used in all of the cases as initial treatment. In 9 cases the test remained persistently strongly positive (+++++) throughout the course of the observation. All of these patients retained a presumably latent focus of their disease with persistent clinical signs. In 21 cases the

test was reversed from strongly positive (+++++) to negative. These patients were clinically and bacteriologically cured. In the group in which the test changed from ++ and + to negative, the serologic reversal occurred sooner than in the group with +++ and ++++ reactions. In 11 cases the test remained negative throughout the course of the disease in spite of the presence of an active infection. A negative serologic reaction does not always mean the absence of a gonococcal infection unless it is confirmed by negative clinical or bacteriologic findings.

Positiveness of the flocculation reactions for syphilis in malaria. F. Canova. *Riforma med.*, Napoli. Apr. 1, 1939, 55: 487.

The author works in a hospital in Transjordan. The territory which this hospital serves lies in a higher part of the country in a region free of malaria but it descends to the borders of the Dead Sea to a region where malaria is endemic. He made a study of the flocculation tests for syphilis in a group of patients with malaria. He found that these reactions were frequently positive in patients with congenital syphilis or in those who had had syphilis in their youth and had been cured. In the patients really completely free of syphilis there were few positive results. He concludes that the malaria merely reactivates an old syphilitic reaction and brings out latent and serologically negative syphilitic infections.

Specificity in the serodiagnosis of syphilis. A differential method. Preliminary report. F. Rytz. *Am. J. Clin. Path.*, Baltimore. July 1939, 9: 512.

Various bacterial diseases other than syphilis, as well as certain noninfectious conditions, may give rise to positive serologic reactions, and it has been assumed that heterophile manifestations and protein disturbances are the actual causes of these nonspecific reactions. "Wassermann-fastness" can perhaps be explained on the same basis, although in some cases other factors are probably significant.

The author reports the results of tests on serums from which the bulk of protein was removed with copper sulfate, while the syphilitic antibody or reacting substance remained in solution with only traces of protein. He describes in detail the removal of the serum protein, the serologic technic, the antigen employed, and the emulsification of the antigen.

Flocculation tests on pooled beef serum by the various routine methods are usually positive. After removing the protein from such serum by the procedure described, such tests are negative. After rabbits have been inoculated with flocculate obtained by routine flocculation tests from beef serum and from human syphilitic serum, routine tests on their serum are positive for syphilis. Such falsely positive rabbit serum was invariably negative after removing the serum protein and following the procedure suggested by the author.

False positive routine flocculation tests were induced in negative human serums by means of contamination with *B. coli*. To 1.0 cc. of normal serum was added 0.05 cc. from a broth culture of *B. coli*, and 5 percent of 100 serum samples thus treated were falsely positive to routine flocculation tests after 24 hours incubation at room temperature. After removing the serum proteins and following the test procedures described by the author, all of these serums were negative.

Blood samples from 1,000 patients whose routine tests for syphilis were positive were retested by this method. Of the 1,000 patients, 880 were confirmed as syphilitic, and tests on the remaining 120 were found to be negative. A small percentage of the 120 patients had acute infections, malaria, lead poisoning, or rheumatic fever—no history of syphilis but two or more of their routine tests for syphilis were positive. Antisyphilitic treatment was given to none of these patients, and routine tests made from their serums eventually were negative. The majority of the 120 patients had no history of syphilis but had been diagnosed as having "latent syphilis" because

of their positive routine serologic test. Many were given antisyphilitic treatment for 3 years or longer without any apparent change in the serologic reactions and were considered as "Wassermann-fast."

Patients with a diagnosis of neurosyphilis were not considered in this work.

Serodiagnosis of syphilis by means of dried blood: The Bordet-Wassermann reaction. R. Demanche and M. Lemaitre. *Bull. Soc. franç. de dermat. et syph.*, Paris. Apr. 1939, 46: 709.

The authors have applied the Wassermann reaction to dried blood. The technic is as follows: Two round pieces of filter paper 24 mm. in diameter are completely saturated with blood obtained by pricking the end of the finger or the ear. The quantity of fresh blood so obtained varies between 0.05 and 0.06 g. The papers are allowed to dry in the air. Each paper is then placed in a hemolysis tube. To the first tube is added 0.6 cc. of cholesterinized antigen and to the second 0.6 cc. of complement which has been diluted with an equal volume of physiologic salt solution. The tubes are tilted to aid in removing the blood from the paper. They are allowed to stand at room temperature for 1 hour. The papers are then removed. Next, 0.6 cc. sensitized red blood cells are added and the tubes placed in a water bath at 37°. Readings are made 15 to 20 minutes later. The test is read by comparing the opacity in the tube tested with the perfectly clear control tube.

By means of this test the blood of 44 patients was examined, together with the usual Wassermann, Kahn, and Meinicke reactions. In 127 there was complete agreement of all three tests, the result being all negative. In this group 1 were nonsyphilitics, 2 had early chancre and 22 had old, treated infections. There were 273 reactions which were positive with at least 1 test. In this group the dried blood method gave 209 positive reactions. There were 64 more positive reactions with the flocculation tests and more positive reactions with the regul-

Wassermann test. The authors state that the object of this study was to show that dried blood can be used in the Wassermann reaction but do not advocate using it to replace the regular Wassermann reaction.

the incidence of congenital syphilis. B. Kemkes. *Ztschr. f. Kinderh.*, Berlin. June 6, 1939, 61: 121.

In Frankfurt am Main 7,632 children were examined by means of the dried blood reaction for syphilis, using the Ehrlich modification of the original Chevalet method. The total number included a group of 7,082 public school children between the ages of 6 and 14 years, of whom 745 were retarded, a group of 349 middle school children between the ages of 11 and 18 years, and 201 children in an institution for the deaf and dumb. Whenever a positive reaction was obtained a second test was made and if this was again positive the usual serologic reactions for syphilis were carried out and a family history was obtained. Among the 745 retarded children 8 (percent) were found to have congenital syphilis. Four of these had already been diagnosed, the other 4 were discovered by this group testing. Of the 201 deaf and dumb children 2 (1 percent) had congenital syphilis. In the group of 7,082 public school children 14 positive tests (0.22 percent) were obtained. Of these, 7 were known cases of congenital syphilis and 7 were discovered through this test. The test was negative in all of the 349 middle school children. By means of family investigations in 12 cases, 5 cases of congenital syphilis were diagnosed which had not been previously diagnosed and in which the dried blood test had been negative. Altogether, therefore, 0.3 percent of congenital syphilis was found among the entire group of 7,632 school children.

The author concludes that a systematic and comprehensive campaign against syphilis should be carried out and that such a campaign is in every way feasible.

TREATMENT

The treatment of gonococcal vaginitis by estrogenic hormone. Adolph Jacoby, Dominic E. Madonia, Sol M. Till and Thornton H. Wood. *Am. J. Obst. & Gynec.*, St. Louis. July 1939, 38: 140.

To determine the value of the estrogenic hormone in the treatment of gonococcal vaginitis a study was undertaken in three of the social hygiene clinics of the department of health in New York City. In all, 108 patients were treated and observed for a sufficient period to report results. The diagnosis was based upon the presence of purulent vaginal discharge and gram-negative intracellular diplococci in the smear. No cultural diagnosis was employed. Amniotin in capsules containing 1,000 international units was inserted into the vagina every night. The patient continued treatment until all clinical evidence of the disease disappeared. Smears at weekly intervals were taken in all cases. Treatment was discontinued when the clinical signs disappeared and numerous successive smears were taken for a period of 2 months. The minimum number of smears was 6 from each patient. When smears became negative, observation of the patient was continued for 6 months longer. Of the 108 patients treated, 92 (85 percent) appeared to be cured after an average of 149 days. Sixteen patients were never cured.

The favorable results of the treatment with the follicular hormone, as reported by various observers, have been attributed to the production of a mature type of vaginal mucosa. This explanation, the authors say, fails to take into consideration that the cervix is involved and that the cervical infection often invades the parametrial lymphatic vessels. The possibility remains that the disease in those who seem to be cured may only be dormant. The large percentage of re-

lapses would indicate that phagocytic destruction of the gonococci in the submucosa does not occur in a large number of patients. Adult females may harbor the gonococci in the tissues for long periods of time and act as sources of infection.

The vaginal acidity varied greatly among positive smears.

The authors feel that although the treatment with amniotin capsules is simple and produces no apparent permanent physiologic damage, the results so far obtained are not conclusive. The uncertainty of the ultimate results with this treatment indicates the necessity for prolonged follow-up in those apparently cured. The desirability of more intensive efforts to determine when cure is established is obvious, and investigation for this purpose, along with other phases pertaining to this disease, is urgently needed.

Sulfanilamide in the treatment of gonorrhea. Adolph Jacoby, Alvin C. Drummond and Arthur H. Ollswang. *New England J. Med.*, Boston. July 20, 1939, 221:102.

Results of treatment of 100 gonorrhea patients with sulfanilamide alone are reported; 45 percent were cured in an average of 13.7 days. Of 23 patients treated with sulfanilamide and vitamin C, 48 percent were cured in an average of 11 days. Of 43 patients treated with a combination of sulfanilamide and gonococcal vaccine, 81 percent were cured in an average of 19.3 days.

It appears from these results that to enhance the action of sulfanilamide by adjuvant therapy which either increases the antibody formation or increases the efficiency of sulfanilamide, is a promising method of treatment. Further studies will be needed before precise information becomes available.

The advantage of combining treatment is also shown in the much lower incidence of reactions to sulfanilamide requiring discontinuance of treatment. Only 14 percent of the patients taking full doses of sulfanilamide and vitamin

C and 11 percent of those taking sulfanilamide and vaccine had toxic reactions following treatment, compared with about 25 percent of those taking sulfanilamide alone in equivalent doses.

Criteria of cure included the absence of symptoms and signs; repeated negative smears and cultures from the urethra, cervix, prostatic secretions, and urinary shreds; provocative instillation of silver nitrate; passage of sounds in men; the drinking of alcoholic liquor followed by negative smears and cultures; and protected sex contact followed by negative smears and cultures.

Solu-salvarsan. Toxicological and therapeutic tests made in behalf of the Therapeutic Trials Committee of the Medical Research Council. L. W. Harrison. *Brit. J. Ven. Dis.*, London. July 1939, 15: 203.

Solusalvarsan was submitted to the committee in 1933 for investigation prior to application being made for a license to import it into Great Britain. The results of this investigation by the members of the committee suggested that the advantages of convenience of administration and of comparative freedom from discomfort after intramuscular or deep subcutaneous injections of solusalvarsan were more than offset by the higher incidence of toxic effects, particularly dermatitis, following its administration, and by its lower therapeutic effect as judged by its ability to cause the disappearance of *S. pallida* from the discharge of early lesions. The investigation was continued in 1938 by five members of the committee. Each treated a small number of patients who had early syphilis with three doses of 5 cc. each per week for 3 weeks, no other remedy being given.

All those who collaborated in this investigation agreed that the therapeutic power of solusalvarsan, weight for weight, was quite distinctly less than that of neoarsphenamine. Toxic reactions were unduly frequent. A total of 4 cases were treated and dermatitis was recorded in 12, jaundice in 3, and herpes of the face in 1. The toxic effects were

arently not due to excessive dosage. Comparison reviews references from the literature, from which weaker therapeutic action and greater toxic action are shown in solusalvarsan than from neorsphenamine. In view of such important disadvantages there seems to be no indication of its use in the treatment of syphilis.

Pathology of general paresis and of tabes in relation to the duration of the infection and the effect of treatment.

J. Spillmann, Aubry, P. Michon and A. Spillmann. *Ann. de mal. vén.*, Paris. June 1939, 34: 343.

Among a group of 159 patients with general paresis observed by the authors there were 87 who were entirely unaware of their syphilitic infection and who had received no antisyphilitic treatment. There were 24 who, although aware of their infection, had either had no treatment or had been treated very late, namely 12 to 14 years after infection. They found the average incubation period for general paresis to be 13½ years. There were 43 patients who had received the early treatment, only rarely for as long as 1 year. One of the patients had been treated for 2 years. The average incubation period in this group was 16 years with variations between 4 and 49 years. There were 3 patients who had received prolonged treatment. In these the average incubation period was 9 years. The treatment in these patients, although prolonged, had not been properly planned or adequate; for example, 1 patient had received only mercury by mouth for the first 13 months of infection.

Among 58 patients with tabes there were 32 who were unaware of their infection, and 10 who although aware of the infection, had received no treatment and in whom the incubation period of tabes was an average of 24 years. There were 16 patients who had received little treatment early in the course of the infection. In this group the average incubation period was 12½ years varying between 6 and 22 years. There were 2 patients who received a considerable amount of treatment but too irregularly.

Three cases of taboparesis were observed. The incubation periods were 21, 18, and 14 years.

The impressions obtained from this study are that inadequate treatment tends to shorten the incubation period of tabes and paresis. Neither general paresis nor tabes was observed in patients who had been given adequate treatment in the primary or secondary stages of syphilis.

Mapharsen in the treatment of early syphilis. Comparison of results in 188 cases with those of the Cooperative Clinical Group. Louis Chargin, William Leifer and Theodore Rosenthal. *Arch. Dermat. & Syph.*, Chicago. Aug. 1939, 40: 208.

The need for a drug of high therapeutic efficiency and minimal toxicity and with facility of preparation and administration, is of vital importance for the ultimate eradication of syphilis. Among the drugs recently introduced, mapharsen seems most nearly to meet these requirements. Its manufacturers claim that it is a pure and stable chemical; it has low arsenic content in therapeutic doses; it has a high therapeutic efficiency in human beings as well as in animals; it is readily soluble, easy to administer, and has relatively low toxicity.

The authors undertook a study, the purpose of which was to determine the efficacy of mapharsen against early syphilis and to compare the results with those obtained by the most effective method of therapy now in use. The total series comprised 215 cases, of which only 188 were followed long enough to allow a fair evaluation of the therapeutic efficiency of the drug. The period of observation varied from 12 to 42 months, 135 (71.8 percent) having been observed for 18 months or longer.

The continuous method of treatment advocated by the Cooperative Clinical Group was followed in all cases. For most of the patients the maximal recommended dose was used—for males 0.06 gm. and for females 0.04 gm. In all cases 10 percent bismuth subsalicylate in

oil was given in doses averaging 1.5 cc. per injection.

A comparison of results is made with those obtained by the Cooperative Clinical Group in their series of 169 cases of early syphilis treated similarly but with arsphenamine or neoarsphenamine and observed for 2 years or longer. In the authors' series satisfactory results were obtained in 158 cases (84 percent) and unsatisfactory results in 30 (16 percent), as compared with 134 (79.3 percent) satisfactory results and 35 (20.7 percent) unsatisfactory in the other group. The difference between the percentages for the two groups is so small that the authors consider it insignificant. Since the authors' patients were observed for a shorter period than those in the other group, it is possible that a small percentage of their cases will be found, on further observation, to be unsatisfactory, but the authors do not think it likely that the number of such cases would be large enough to alter the results materially.

The toxicity in this series was minimal, consisting chiefly of immediate reactions (pain in the arm, dizziness, nausea), and in practically every case the treatment with mapharsen could be continued. The rarity of cutaneous eruptions resulting from mapharsen was remarkable. No exfoliative dermatitis occurred.

There was noteworthy parallelism in the results with the two groups; the best results were obtained with the disease in the seronegative primary stage, the next best with the secondary stage, and the least satisfactory with the seropositive primary stage.

The authors are of the opinion that the results obtained with mapharsen in the treatment of early syphilis appear to be as satisfactory as those obtained with other effective arsenicals when the same method of therapy is used and that the favorable results justify further trial on a more extensive scale with careful, prolonged observation.

Treatment of gonorrhea in private practice. Robert Forgan and H. P. Newsholme. *Brit. M. J.*, London. July 15, 1939, 2: 138.

In this letter to the editor, Forgan states that specialists have been able to lay down certain broad rules for the use of the sulfonamide drugs in cases of gonorrhea but that they have not yet decided questions of optimum dosage and reliable tests of cure. It is painfully evident to these specialists that the rules are unknown or unobserved by practitioners who have neither the facilities nor the training for making accurate diagnoses or tests of cure.

Newsholme states that in the majority of cases of gonorrhea the symptoms of the disease will quickly disappear with sulfonamide therapy, but this does not mean that the patient is cured. Frequently such a patient is a "carrier" of the disease. Practitioners are urged not to discharge a patient as cured until proper tests of cure have been made and the patient has been under observation for at least 3 months after cessation of treatment. Tests of cure should include the examination of at least 3 smears and 3 cultures. Smears alone are not reliable. A blood examination, Wassermann test, and gonococcal complement fixation test should be made in each case. If the practitioner cannot make the necessary cultures, the patient should be referred to a venereal disease clinic, where the tests may be made and reported to the practitioner. Patients taking any of these drugs should be watched carefully for gastric symptoms, dermatitis, leukopenia, or any other signs of toxemia resulting from the treatment.

Forgan states that the percentage of defaulting patients with gonorrhea has risen sharply since the introduction of the sulfonamide drugs. However, if these drugs are wisely used early in the course of the disease, and if every patient is closely observed until cure is certain, the result should be a fall in the incidence of gonorrhea vastly greater than

mat of syphilis (in England) during the last 20 years. Some measure of legal compulsion will probably be required before gonorrhea is finally conquered.

Four hundred and seventy-three hospitalized male gonorrhea patients treated with sulfanilamide. J. R. Waugh and T. R. Dawber. *Am. J. Syph., Gonor. & Ven. Dis.*, St. Louis. July 1939, 23: 477.

During the 18-month period from June 1937 to November 1938, a total of 473 male gonorrhea patients (327 white and 146 Negro) were treated at the U. S. Marine Hospital (Norfolk) with sulfanilamide and without local urethral or prostatic treatments. All of them were hospitalized during the course of their treatment and during the time required to complete the necessary laboratory tests—a total of approximately 3 weeks. Most of the patients were otherwise healthy and between 20 and 30 years of age. Criteria of cure included (1) cessation of discharge; (2) clear urine in both glasses with only a very few shreds (2-glass test); (3) prostatic smear and culture negative for gonococci; (4) urethral smear negative for gonococci, provided a drop appeared on the morning after the provocative passage of a steel sound the whole distance into the bladder, followed by the instillation of 0.5 percent mercurochrome or 1:4,000 acriflavine solution.

The dosage of sulfanilamide was 120 grains in 4 divided doses for the first 24 hours and then 60 grains in 4 divided doses daily for 14 days longer. Seventy-five percent of the 473 patients completed

the full 15 days of treatment, and about 65 percent of the total number apparently recovered completely. There were 73 percent apparent recoveries among the Negro patients compared with 61 percent among the white patients. Of those who had acute infections (less than 28 days duration) 65 percent recovered while 63 percent of those with chronic infections recovered. Of the patients whose treatment was instituted during the first week of the infection, only 58 percent were cured. Of the group who were given treatment beginning in the second, third, or fourth week after onset of the disease, about 70 percent recovered.

Of the patients who were given the drug for 3 to 7 days, 37 percent recovered; and of those who were given the drug for the full 15 days, 71 percent recovered. Of the patients with complications (not including prostatitis) at the time of admission, 90 percent recovered; while only 64 percent of the patients without complications recovered.

Of the 473 patients, 10.9 percent had severe reactions, and 8 percent of the patients were forced to discontinue treatment for this reason. Toxic effects sufficiently serious to warrant cessation of treatment included dermatitis, fever, anorexia, nausea or vomiting, abdominal pains, diarrhea, mental confusion, severe anemia, severe anemia with jaundice, and granulocytopenia with angina. There were no fatalities.

Of the 314 patients on whom blood counts were made, 17.5 percent had some degree of anemia, but only 3.2 percent had counts below 3.5 million red blood cells.



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FEDERAL SECURITY AGENCY
UNITED STATES PUBLIC HEALTH SERVICE
Thomas Parran, *Surgeon General*

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CORRECTION: Venereal Disease Information, Aug. 1939, 20 :
231—The name of one of the authors of "Practical epidemi-
ology of gonococcic infections in children" should have been
given as Joseph Weinstein instead of Jacob Weinstein.

Spirochete Counts in Fluid from the Surface Lesions of Early Human Syphilis

GEORGE VRYONIS, M. D. and HUGH J. MORGAN, M. D.

Nashville, Tennessee

INTRODUCTION

PUSEY IN 1933 emphasized the practical importance of knowledge concerning the abundance or scarcity of *Spirochaetae pallidae* in the various lesions of syphilis (1). The number of organisms present in surface lesions probably plays a definite part in determining their infectiousness or noninfectiousness. Fluid is the medium by which these organisms are transferred from the surface of the infectious lesion to the skin or mucous membranes of the new host. Thus, the number of spirochetes present in fluid from moist lesions is the chief point of interest in a consideration of the infectiousness of the different skin and mucous membrane lesions of syphilis.

Leipold (2) in 1926 estimated the number of spirochetes per dark field in chancre fluid. By using a special pipette, he placed a standard sized drop of fluid under a cover slip of standard size. He counted the spirochetes in 200 fields and determined the average number per field. This method is useful in estimating the relative number of organisms in different specimens of fluid, but it gives no information regarding the actual number per unit of fluid.

A practical method is available (3) for the enumeration of spirochetes in a fluid menstruum, and in the present study this has been utilized to determine the actual spirochete counts in fluid obtained from the surface lesions of human syphilis.

NOTE.—From the Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee. This work was made possible by a grant from the United States Public Health Service.

MATERIAL

The patients for this study were obtained from the clientele of the syphilis clinic of the Vanderbilt University Hospital. No selection on the basis of age or race was made. Patients who exhibited lesions of early syphilis which were suitable for dark-field examination were accepted for the study. Counts were made on 53 specimens from 39 patients.

METHOD

Specimens of fluid.—The procedure for obtaining the specimen was adapted to the individual lesion. Moist lesions were mopped vigorously with dry gauze. As fluid reaccumulated, 2.75 cubic millimeters were collected in a micropipette by capillary attraction. When fluid could not be readily obtained, the lesion was lightly scraped with a scalpel. Those lesions covered with epithelium were cleansed, dried, and scraped with a scalpel until slight bleeding occurred. The denuded surface was then blotted with dry gauze until blood ceased to appear. Under these circumstances fluid promptly accumulated as a rule, though at times it was necessary to squeeze the lesion between the thumb and index finger.

Spirochete counts.—The standard unit of tissue fluid in the calibrated micropipette was placed on a glass slide under a cover slip of known dimensions. The spirochetes present in a certain number of optic fields of known size were counted, using dark-field illumination. The total number of organisms per cubic

millimeter of fluid was then calculated. The method has been described in detail elsewhere (3).

RESULTS

The data in table 1 are given in the order obtained. It is seen that spi-

rochete counts were made on fluid obtained from "active" and recently "healed" chancres, genital and perianal condylomas, mucous patches, secondary extragenital lesions of the skin and from lesions in recurrent early syphilis (mucocutaneous relapse).

TABLE 1.—The number of *Spirochaetae pallidae* per cubic millimeter in fluid from the lesions of 39 patients with early syphilis

Case No.	Date	Sex	Age	Race	Type of lesion	Location of lesion	S. pallidae per cubic millimeter
1938							
1	Apr. 14	M	24	White	Chancre, "healed"	Prepuce	12,500
2	Apr. 15	M	18	do	Chancre	Shaft of penis	3,600
3	Apr. 21	F	19	Negro	Condyloma	Labium	13,300
4	Apr. 22	F	do	do	do	do	246,000
5	July 15	F	20	do	do	do	37,000
6	July 23	F	16	do	do	Vulva	9,300
6					Chancre, "healed"	Labium	21,700
7	Aug. 4	M	42	White	Chancre	Glans penis	10,000
8	Aug. 16	M	23	do	do	Shaft of penis	34,000
9	Aug. 17	F	18	do	Annular ulceration	Right ante-cubital fossa	2,300
9					Papule, dry	Perianal	3,200
9					Ulceration, flat	Axilla	8,500
10	Sept. 14	M	17	White	Chancre	Prepuce	29,500
11	do	M	51	Negro	Annular, dry	Forehead	1,500
11					Papule, dry	do	740
12	Sept. 21	F	38	Negro	Condyloma	Labium	16,400
13	Sept. 23	M	25	do	Ulceration, scaly, dry (healing)	Thigh	370
13					Ulceration, flat	do	9,200
13					do	Leg	4,200
13					Mucous patch	Lip	13,000
14	Sept. 24	M	45	White	Moist flat	Thigh	2,500
15	Oct. 7	F	32	do	Mucous patch (relapse)	Lip	8,000
16	Oct. 11	M	18	Negro	Condyloma	Perianal	35,300
17	Oct. 21	F	19	do	Chancre	Lip	2,700
18	Oct. 22	F	23	do	Healing, dry	Perianal	2,300
19	Oct. 28	F	20	do	Condyloma (relapse)	Labium	24,800
20	Oct. 29	M	23	do	Ulceration, flat (relapse)	Glans penis	6,800
20					Ulceration, flat, dry (healing)	do	900
21	Nov. 1	M	28	White	Chancre	Prepuce	2,500
22	Nov. 8	F	16	Negro	Condyloma	Labium	3,700
23	Nov. 10	F	18	White	Mucous patches	Mouth	34,000
23					do	Lip	37,400
24	Nov. 11	M	53	Negro	Condyloma	Perianal	34,000
25	do	F	19	do	do	Labium	12,000
25					Mucous patch	Lip	30,000
26	Nov. 11	F	25	Negro	Chancre, "healed"	Labium	9,000
27	do	M	23	White	Mucous patch (relapse)	Tongue	11,000
28	Nov. 29	F	14	Negro	Papule, ulcerated	Axilla	740
28					Condyloma	Labium	63,000
29	Dec. 1	F	20	Negro	do	do	24,000
30	Dec. 3	M	26	White	Chancre	Glans penis	370
31	Dec. 8	F	16	Negro	Condyloma	Labium	30,000
32	Dec. 13	M	20	do	Mucous patch	Lip	9,200
33	Nov. 25	F	18	White	Chancre	Vulva	10,000
34	Nov. 26	M	15	do	do	Prepuce	17,000
35	Dec. 20	F	15	Negro	Condyloma	Labium	38,000
35					do	do	33,000
35					do	do	15,000
35					do	do	23,000
1939							
36	Feb. 1	M	26	Negro	do	Perianal	23,000
37	Feb. 2	M	26	do	do	do	22,000
38	Feb. 3	F	25	White	Chancre	Labium	25,500
39	do	M	24	Negro	Condyloma (relapse)	Perianal	8,000

The counts on the specimens from all lesions varied between the extremes of 370 spirochetes per cubic millimeter in fluid from the scaly scar of a healing

secondary lesion and 246,000 per cubic millimeter in a specimen of condyloma fluid. It is seen that the counts on fluid from several lesions in the same

patient varied greatly. In case number 6, fluid from the epithelialized chancre contained more spirochetes than fluid from a condyloma of the labium. In case number 13 fluid from a dry healing skin lesion (thigh) contained 370 spirochetes per cubic millimeter, and two moist lesions on the lower extremity contained 9,200 and 4,200 per cubic millimeter, respectively. Fluid from a flat ulcerated lesion on the glans penis in case number 20 contained 6,800 spirochetes per cubic millimeter while an adjacent healing lesion yielded only 900. A moist lesion in the axilla of patient number 28 yielded fluid which contained 740 spirochetes, whereas the condyloma fluid from the same patient contained 63,000 organisms per cubic millimeter. Four condylomas in patient number 35 afforded specimens of fluid which varied in spirochete content between 15,000 and 38,000 per cubic millimeter.

It seems evident from table 1 that age and race exert little, if any, influence upon the number of spirochetes present in fluid from comparable lesions. However, genital condylomas occur most frequently in Negro women, and it is this type of lesion, in our experience, which yields fluid richest in *S. pallidae*. Special attention should be directed to cases number 15 and 39. Patient number 15 was seen at the syphilis clinic of the Vanderbilt University Hospital in April 1934 because of a lesion (presumably a chancre) of the tongue. A

single dark-field examination proved negative. The Wassermann reaction of the blood was positive. After she had received 2.4 gm. of neoarsphenamine and 0.6 gm. of bismuth salicylate, the lesion disappeared and she refused further treatment. In October 1938 she returned to the clinic. Mucous patches were present in the mouth, and fluid from one of them contained 8,000 *S. pallidae* per cubic millimeter. Patient number 39 stated that 5 years previously he had had a painless lesion on the penis which was followed by a generalized skin eruption. The Wassermann reaction of the blood was positive 30 months before his admission to the hospital in February 1939 with small perianal condylomas. The spirochete count on fluid from a condyloma was 8,000 per cubic millimeter. Three other patients with recurrent acute syphilis were studied. All had acquired the disease within a year of the time of our examinations.

In order to compare the spirochete counts on fluid from the several types of lesions studied, table 2 was prepared. It summarizes the content of table 1. In it are recorded the number of lesions examined and the maximal, minimal, and average number of spirochetes in a cubic millimeter of fluid from the different varieties.

It is seen that as a group the condylomatous lesions yielded fluid which contained the greatest number of *S. pallidae*. Fluid from mucous patches

TABLE 2.—The number of *Spirochaetae pallidae* per cubic millimeter in fluid from the lesions of 39 patients with early syphilis (summary of table 1)

	Chancres ¹		Condylomas		Mucous patches (oral)	Moist extra-genital skin lesions	Dry secondary lesions ²	Moist lesions of recurrent early syphilis (mucocutaneous relapse) ³
	"Active"	Epithelialized	Genital	Perianal				
Number of lesions examined.....	9	3	14	4	5	6	6	5
Highest count per cubic millimeter...	34,000	21,700	246,000	35,500	37,400	9,200	3,200	24,800
Lowest count per cubic millimeter...	2,500	9,000	3,700	22,000	9,200	740	370	6,800
Average count per cubic millimeter...	14,900	14,400	40,200	28,600	24,700	4,500	1,800	(11.7)

¹ Fluid from one neoarsphenamine-resistant chancre was examined. It is not included in this table. The spirochete count was 370 per cubic millimeter.
² Healing extragenital ulcerations, extragenital papules and annular lesions, perianal papules, and a dry ulceration of the glans penis (relapse).
³ Lesions of lips, genitals, and perianal region.

and chancres gave consistently high counts. Fluid from "healed" (epithelialized) chancres contained approximately the same number of organisms as that from "active" chancres. The moist extragenital skin lesions of secondary syphilis yielded a smaller number of organisms than moist genital, perianal, and oral lesions. Fluid from dry lesions of the skin contained fewer spirochetes than fluid from any other lesions. The lesions of recurrent early syphilis (muco-cutaneous relapse) yielded fluid which was on the average somewhat less rich in *S. pallidæ* than the secondary lesions of similar type and location in uncomplicated early syphilis. Nevertheless, a high count was obtained from a genital lesion of this type.

DISCUSSION

Neisser (4) observed that success in transmitting syphilis to monkeys by means of inoculation with chancre fluid was related to the number of *S. pallidæ* in the inocula. However, this is not the sole factor which determines the development of the disease. Our experience with the injection of varying numbers of organisms in rabbits (5) indicates that only a small number of *S. pallidæ* are necessary to induce syphilis in some animals. We have been able to cause the formation of typical chancres with inocula containing only 100 organisms. Nevertheless, it is known that in some rabbits much larger doses of the virus may fail to result in the development of disease. Thomas and Morgan (6) were unable to induce chancre or other evidence of infection in 16 rabbits by the intratesticular injection of from one to six *S. pallidæ*. Thus, it seems clearly established that more than one organism must be inoculated to induce infection and that within rather wide limits a minimal infecting dose exists for syphilis in the rabbit. It is apparent that the minimal infecting dose varies considerably for the species. This variation in susceptibility to infection together with variations in the size of inocula doubtless play major roles in the epidemi-

ology of the human disease. It is obviously not permissible to draw definite conclusions relative to human syphilis from observations made on rabbits infected with *S. pallidæ*. Nevertheless, it is of interest to note that, if the susceptibility of some persons to infection with syphilis is as great as that of some rabbits we have studied, an inoculum of about 1/150 cubic millimeter of chancre fluid or 1/375 cubic millimeter of condyloma fluid may result in disease.¹

SUMMARY AND CONCLUSIONS

We have determined the number of *S. pallidæ* per cubic millimeter in fluid yielded by 53 surface lesions of early syphilis. The lesions occurred in 35 patients.

The moist lesions of early syphilis yield fluid rich in organisms. The highest counts occurred in condyloma fluid, the extremes on eight specimens being 3,700 and 246,000 *S. pallidæ* per cubic millimeter. Fluid from mucous patches and "active" and "healed" chancres gave consistently high counts. Fluid obtained from six dry lesions of the skin gave the lowest counts, the extremes being 370 and 3,200 organisms per cubic millimeter.

Spirochete counts on fluid from the moist lesions of recurrent early syphilis (muco-cutaneous relapse) varied between 6,800 and 24,800 per cubic millimeter. Two of these patients acquired syphilis presumably 4½ and 5 years before our examination. Both patients had lesions which yielded fluid containing 8,000 organisms per cubic millimeter.

Infection of man by *S. pallida* doubtless depends largely upon the size of the inoculum and individual susceptibility to the disease. Our observations indicate that, if human beings are as susceptible to infection by *S. pallida* as rabbits, they may become infected by as little as 1/375 cubic millimeter of condyloma fluid or 1/150 cubic millimeter of chancre fluid.

¹These calculations are based on the average spirochete counts obtained in fluid from chancres and condylomas. (Table 2.)

- (1) Pusey, William Allan: The history and epidemiology of syphilis. Springfield, Charles C. Thomas, 1933.
- (2) Leibold, W.: Die Wirkung verschiedener Syphilisheilmittel auf die Oberflächenspirochäten. Dermat. Ztschr., 1926, 49: 341.
- (3) Morgan, Hugh J. and Vryonis, George P.: A method for the quantitation of inocula in experimental syphilis. Am. J. Syph., Gonorr. & Ven. Dis., 1938, 22: 462.
- (4) Neisser, A.: Erforschung der Syphilis. Arb. kaiserlichen Gesundheitsamte, 1911, 37: 1.
- (5) Morgan, Hugh J. and Vryonis, George: The influence of the size of the inoculum on the incubation period and clinical manifestations of experimental syphilis. (To be published.)
- (6) Thomas, C. and Morgan, Hugh J.: Single cell inoculations with *Treponema pallidum*. J. Exper. Med., 1934, 59: 297.

give notification of all their cases as the clinics do? (3) Would not notification deter a considerable proportion of patients, through fear of exposure, from seeking adequate treatment? (4) A patient cannot be compelled to take treatment if he cannot be located; if he gives a false address, how can he be found?

The annotator states that even if the compulsory system works well in Scandinavia it does not follow that it would do so in Great Britain, and the average patient in England will not submit readily to forcible treatment of which he does not approve. Few will deny that notification and, if necessary, compulsory treatment are ideal if they can be enforced; but the majority of physicians in England consider that such measures would not be workable at present and that public opinion must be changed by education before they could be successfully introduced. To abolish the voluntary system and introduce compulsory measures before public opinion is ready for it would be to run the risk of a big setback.

Syphilis and mobilization. W. F. Lorenz and W. J. Bleckwenn. Mil. Surgeon, Washington. Sept. 1939, 85: 197.

In Wisconsin there have been 129 cases of neurosyphilis among the veterans of the World War, and this is less than half the number that might be expected from the 140,000 enlistments. Using these cases as a basis, it is estimated that the cost of the care of the ex-service men who became disabled due to syphilis exceeds one hundred million dollars since the World War. During the World War many Wassermann tests were performed, according to the report of the Surgeon General, but these were apparently limited to three or four training camps. It is believed that very few, if any, of the first 250,000 troops mustered into service were ever examined for syphilis beyond the general physical examination attempted in the initial concentration camps. Syphilis exacts a tremendous tax, not only during the period of military activity but as a post-war liability.

PUBLIC HEALTH ADMINISTRATION

Compulsory measures for venereal disease. Annotation. Brit. M. J., London. Aug. 26, 1939, 2: 455.

The report of the British Commission on Venereal Disease sent to Scandinavia and Holland in July 1937 has been criticized by A. W. Towne (Am. J. Syph., Gonorr. & Ven. Dis., May 1939, 23: 348). Towne holds, contrary to the findings of the Commission, that compulsory measures have been largely responsible for the very great decline in syphilis in Scandinavian countries.

In this annotation, the following questions are raised: (1) Would compulsory methods work in England? (2) Would the private practitioner and consultant

With the thought that organization and training were necessary, the authors worked out a plan for a syphilitic survey in the Wisconsin National Guard during the annual field camp. It was decided that the "blood taking" would not be required by orders but would be voluntary on the part of those under military authority, and that, as much as possible, the customary ethics of private medical practice would be maintained. The station was carefully organized; a diagram of the set-up is given as well as the rules for each of the necessary units. Under the plan developed 50 different specimens could be readily examined in the course of 20 to 25 minutes and approximately 100 tests could be performed by each technician per hour.

While no soldier was required to have this examination, only 2 members of the infantry brigade refused. Among 2,682 individuals 14, or 0.5 percent, had evidence of a syphilitic infection. This rate is very similar to that which has been found in the premarital examinations made in Wisconsin, namely, 0.6 percent. None of these persons knew that they were diseased.

The authors believe that the plans they used in their examination of the National Guard demonstrate that the infected person can be discovered at the time he is inducted into service without much outlay of money. They believe that the cost to test the blood from 140,000 persons (Wisconsin quota in 1917) at the rate of 4,000 per day would probably not exceed \$1,200 or \$1,500, which is a very small outlay when compared to the tremendous financial tax upon the government due to undiscovered and untreated syphilis in the soldier.

Neo-natal mortality. Julius Levy. Pub. Health News (New Jersey State Department of Health), Trenton. Aug. 1939, 23: 112.

In a carefully conducted series of 800 autopsies on newborn babies who had had complete Wassermann tests, only 1 percent of the mortality was found to be related to syphilis. In comparing the incidence of various accidents of labor and

pregnancy among syphilitic and non-syphilitic mothers, it was found that only in prematurity of birth was there a higher incidence among the children of syphilitic mothers. The fact that a child had syphilitic lesions or that its Wassermann test was positive is not proof that the child died from syphilis. It might have died from pneumonia, birth injury, or asphyxia.

Some aspects of the public health control of syphilis. J. R. Heller. Texas State J. Med., Fort Worth. Aug. 1939, 35: 305.

This subject is discussed under the headings of personnel, diagnostic facilities, treatment, premarital and premarital certificates, reporting, postgraduate instruction for physicians, case-finding, case-holding and contact-tracing, education, and the Texas venereal disease program.

Trained personnel is an essential factor in a syphilis control program. Health officers should not remain as clinicians in treatment services, but should devote their time to other phases of the program. Diagnostic facilities should conform to recommended standards of the Committee on Evaluation of Serologic Tests for Syphilis (U. S. Public Health Service) and certification of laboratories is urged. Modern accepted treatment measures should be followed in all cases.

Prematernal and premarital examination laws will contribute to the success of the program. Proper reporting of cases is now lagging, but the use of simpler report forms in the future may stimulate physicians to report all cases. Application of the procedures of case-finding, case-holding, and contact-tracing helps to reduce syphilis to the status of other communicable diseases. Postgraduate instruction for the physician in the management of this disease should be easily available. Education of the public must be continuous.

Approximately 70 out of 254 counties in Texas are participating in an arrangement made with county medical societies to furnish antisyphilitic drugs free to private physicians for patients unable to

pay the regular fee. Texas has made a good beginning in syphilis control, but additional financial aid and other public support must be forthcoming.

Maternal education the root of the congenital syphilis problem. R. A. Vonderlehr. Health Officer. (Multilithed) U. S. Pub. Health Serv., Washington, July-Aug. 1939, 4: 118.

It is estimated that each year 60,000 babies are born with syphilis, in addition to 25,000 stillbirths. At least half of the deaths are needless if scientific knowledge is applied to the control of syphilis. The chances that a healthy, noninfected child will be born of a syphilitic mother are less than one in six, but if treatment is started before the third month of pregnancy that ratio can be reversed to 10 healthy children out of every 11 born. There are at least a million potential mothers in the United States infected with syphilis. The job that the health officer and the venereal disease control officer has is more than providing treatment for those who apply at the clinics. Persons who need examination and treatment must be brought to the clinic. The need for education that will bring every potential mother to the physician or to the prenatal clinic early in pregnancy cannot be overstressed.

The fight against congenital syphilis in Germany. B. Spiethoff. Deutsche med. Wchnschr., Leipzig. July 28, 1939, 65: 1207.

While prevention is important in all forms of syphilis it is particularly so in the congenital form. For the prevention of congenital syphilis marriage must be protected from the disease. This can best be done by making it possible for young people to marry early. In Germany loans are made to young people who want to marry in order to encourage matrimony. Loans are also made for the care of children. The prevention of unemployment also contributes to this end. Every measure that helps young people to marry early helps to prevent venereal disease. In the

younger age groups in Germany there are twice as many cases of syphilis among the unmarried as among the married. The marriage loans are not made to young people unless they can present a certificate of freedom from venereal disease. This law has been extended so that all candidates for marriage must be free of venereal disease.

The physician must decide whether a patient who has suffered from venereal disease is still infectious. The patient with acquired syphilis is generally considered no longer infectious 4 years after the infection or 2 years after the end of a successful treatment. Women may infect their children 10 to 15 years after an infection. But as they can be treated and the children protected it is not necessary to make them wait so long as this for marriage. According to the law of 1927 every individual who has a venereal disease which is suspected to be in the contagious stage can be compelled to take treatment. If a syphilitic woman is about to be married, therefore, she can be compelled to take treatment.

If the disease has not been prevented by treatment of the mother, treatment should be given the child as soon as possible. In 1927 about 7,000 children were treated in Germany for congenital syphilis, in 1934 only about 4,000. This would indicate that congenital syphilis has decreased more than the acquired form. But one factor has been overlooked. Treatment has rendered the manifest forms less frequent and the nonspecific dystrophic and endocrine forms more frequent; these forms are frequently overlooked so the decrease in congenital syphilis is probably not actually so great as it apparently is. Probably greater progress can be made in detecting these forms of congenital syphilis. There are some signs such as very low (2500 gm.) or very high (over 4500 gm.) birth weight, heavy placenta (more than $\frac{1}{3}$ the weight of the fetus), the so-called little-finger sign of Du Bois, the clavicular sign of Higoumenakis and bed-wetting beyond the third year which are very significant in the diagnosis of congenital syphilis. Congenital syphilis can

be demonstrated in 20 to 35 percent of children with these signs. When these signs become known to the general practitioner congenital syphilis will be diagnosed much more frequently than it now is. School physicians should also be familiar with them.

Chediak's dry blood test should be used for school examinations, since the taking of a drop of blood arouses no suspicion and the method is cheaper than the other methods for mass examinations. This test is positive in more cases than the original Wassermann and in as many as the Kahn reaction. Of course a positive Chediak test must be confirmed by a positive Wassermann. This test should also be used for pregnant women.

Sellar-Kuba's modification of the M. K. R. II has been claimed to be specific for congenital syphilis but the author has not found it so.

Report of committee on control of syphilis. Reports for 70th annual session of the Medical Society of Virginia. Virginia M. Monthly, Richmond. Sept. 1939, 66: 551.

During the fiscal year ended June 30, 1939, the program for the control of venereal diseases in Virginia has expanded. The educational program has been increased for both the laity and physicians. In 1936 there were 19 venereal disease clinics in Virginia; in 1939 there were 99 with a total of 142 clinic sessions each week. Clinics were visited by a member of the division of venereal disease control, and recommendations were made to increase the efficiency of the local control program. The majority of the clinics are following standardized treatment procedures, and the idea of continuous treatment is growing rapidly. Five laboratories supply free laboratory work.

The free distribution of antisyphilitic drugs for the treatment of all cases of syphilis regardless of the patient's economic status was begun Oct. 10, 1938. In order to secure free drugs the case must be reported or designated as previously reported. Arsphenamine, neoarsphenamine, sulfarsphenamine, ma-

pharsen, bismuth subsalicylate in oil, and triple distilled water are made available. From Oct. 1938 to June 1939 the drugs distributed cost \$35,620.52, and were supplied to 2,760 physicians and 638 hospitals and clinics. State and Federal institutions purchase the drugs at cost. A total of \$53,018.26 was expended for the purchase of drugs.

There is noticeable improvement in contact investigation procedure. Physicians record the names of contacts on the reverse side of their report, and the local health department follows up the contacts. There were 6,875 case reports made during the year, 640 (9.31 percent) gave information about their contacts, and 438 were disposed of satisfactorily. There were 9,992 social service visits made to contacts.

The new system of reporting, the better contact investigation, and free antisyphilitic drugs have produced an increase in the number of cases reported, (20,004 cases of syphilis and 3,500 of gonorrhea). There were 32,766 serologic tests made for syphilis, 204 dark-field examinations, 1,749 tests for gonorrhea, and a total of 114,410 clinic visits during the year.

Report of the Committee on Conservation of Vision of the Indiana State Medical Association. J. Indiana M. A., Indianapolis. Sept. 1939, 32: 532.

The above committee recommends that: (1) The question on the State birth certificate, "were precautions taken against ophthalmia neonatorum" be changed to read, "What preventive for ophthalmia neonatorum did you use? If none, state the reason." (2) Legislation should be enacted specifying that only a prophylactic agent (to prevent ophthalmia neonatorum) approved by the State board of health should be used in Indiana. (3) One percent silver nitrate should be used in beeswax ampules as a universal agent for ophthalmia neonatorum at present, with the reservation that this recommended drug may be changed later. (4) The State board of health shall acquaint physicians, individuals, and hospitals with this recom-

mendation to see that the drug is uniformly easily available in the State. (5) The State board of health shall carry on a campaign urging prompt and early reporting of ophthalmia neonatorum as the law now specifies. (6) The State board of health shall request prompt reporting of cases of conjunctivitis of the newborn from whatever cause; and it shall have jurisdiction over these cases until they are definitely classified as not having ophthalmia neonatorum. (7) Consultation with oculists should be urged in these cases whenever such consultation is available. Provisions should be made for expert ophthalmologic and nursing care without delay in all cases.

It is urged that the above recommendations be adopted by the House of Delegates of the Indiana State Medical Association, transmitted to the Indiana State Board of Health, and appropriate State legislation be enacted at the next session of the State General Assembly. The delegates of the Indiana State Medical Association to the annual meeting of the American Medical Association in 1940 should be instructed to present a resolution embodying similar recommendations to be adopted by the States throughout the Nation.

Analysis of Alabama's proposed prenuptial legislation. J. N. Baker. J. M. A. Alabama, Montgomery. Sept. 1939, 9: 91.

A bill introduced into the House of Representatives of the Alabama State Legislature and defeated by the narrow margin of 6 votes (44 to 38) on August 10, 1939, would have required women who were applicants for marriage licenses to obtain physicians' certificates attesting to their freedom from venereal diseases in a communicable stage (laboratory tests for syphilis were required) before they could be married. Such a law already exists in Alabama for male applicants for marriage licenses.

Some persons had the impression that the required physical examination would prove embarrassing for the bride. The examination would prove no more embarrassing than one for life insurance.

A new bill, similar in all essential respects to the one that was defeated, has been introduced in the Alabama State Senate and is waiting legislative action. The author presents an analysis of the proposed measure and a verbatim copy of the bill and certificate forms required.

Gonorrhea. J. M. A. Alabama, Montgomery. Sept. 1939, 9: 98.

For the past few years syphilis has been the only disease treated in the venereal disease clinics of Alabama. Since gonorrhea is probably twice as prevalent as syphilis, it has been suggested that beginning July 1, 1939, all clinics should also treat patients with gonorrhea. Sulfanilamide is supplied free to clinics only. This therapy should be followed by irrigations and instillations if there is little or no clinical response to it. A suggested 8- to 10-day routine treatment for an adult is (1) 20 grains of sulfanilamide 3 times a day and 30 grains at bedtime, (2) one-half teaspoonful sodium bicarbonate taken with each dose of the drug, (3) a maximum fluid intake of about 2 quarts a day.

Mimeographed instructions for patients are supplied to all county health departments. Instead of calling the drug sulfanilamide it is called para-aminobenzenesulfonamide with the hope that patients will be swung away from the drug store purchase of the agent.

Since patients being treated for gonorrhea will probably be seen only once a week, it is suggested that mimeographed instructions on toxic reactions be given each patient. He should be warned to stop taking the tablets if he has a high fever, a rash, a "knocked-out" feeling, or if his lips and face become blue.

Report of the Subcommittee on Stillbirth Registration and Certification. Canad. Pub. Health J., Toronto. Sept. 1939, 30: 457.

The work of the Subcommittee on Stillbirth Registration and Certification of the Committee on the Certification of Causes of Death (Canadian Public Health Association) has to date been

concerned with the institution of a single standard form for the registration and certification of stillbirths in Canada. The Committee's final recommendations were presented in its second annual report, and they included the final draft of a single form for the registration of stillbirths, submitted as an acceptable minimum standard for national use in Canada. The Committee's opinion was that questions relating to cause of death on any national standard stillbirth certificate should be closely comparable with those on the standard death certificate. Stress was laid on the provision of sufficient explanatory notes and examples for the guidance of physician, informant, undertaker, and registrar.

The present report discusses progress made toward introducing the above-mentioned uniform standard certificate in Canada, cooperation with the League of Nations Health Organization in securing uniformity in international stillbirth statistics, studies made in stillbirth nosology, and recent developments in the United States. An outline of the causes of stillbirth, tables presenting the causes of stillbirth (by periods of gestation, time of death, and nature of delivery and injury at birth), and a copy of the medical section of the final revision of the United States standard stillbirth certificate (issued early in 1939) are presented.

Of 449 stillbirths occurring in Canada in 1937-38 and studied by the subcommittee, 7 (1.6 percent) were definitely caused by syphilis. Of this number, 6 of the fetuses died before labor (delivery was spontaneous), and one died during labor.

Community health organization. Chapter VII—Syphilis and Gonorrhea Control. Ira V. Hiscock. New York, The Commonwealth Fund. Third edition, 1939, p. 88.

The author discusses case finding, treatment, nursing services, hospitalization, the educational program, personnel, and budget. It is stated that an adequate program for the control of syphilis and gonorrhea should include and corre-

late its public health activities with medical measures, educational measures, recreational and protective social measures, and law enforcement, but only the public health measures and certain phases of medical and educational activity fall directly in the health officer's jurisdiction. In the conduct of the program the municipal health department should endeavor particularly to secure close cooperation with the State and county departments of health, the local medical society, and voluntary public health and nursing agencies. An adequate health department program for combating syphilis and gonorrhea involves early case-finding, adequate treatment for all infected patients, and education of the private physician and the general public.

The premarital law. Peoria Health News. Aug. 1939, p. 2.

Amendments to the premarital examination law in Illinois were adopted at the last session of the legislature to obviate certain difficult situations which have arisen. As amended, the law requires that blood specimens and gonococcus smears shall be examined only in the laboratories approved by the State department of health. It permits the marriage of infected pregnant women, of unwed infected mothers to the fathers of their children, and the marriage of persons having nontransmissible forms of syphilis. In the latter instance, licenses may be issued only on the approval of the director of the State department of public health.

Prenatal blood tests. Peoria Health News. Aug. 1939, p. 2.

A law recently passed in Illinois requires physicians to have blood tests made for syphilis upon every pregnant woman at the time that she is first examined for her pregnancy. Specimens of blood taken for this purpose shall be submitted to laboratories approved by the State department of public health, or such examinations may be made without cost to the physicians at the laboratories of the State health department.

The law provides, further, that in reporting births and stillbirths, physicians shall record on the required certificate whether or not such tests of the blood of the mother have been made, but in no case shall the results of the test be stated on the certificate.

Rules and regulations regarding premarital examinations for syphilis. Health News (Supplement), Albany. Aug. 14, 1939, 16: S-33.

Administrative rules and regulations in connection with the amendment to the domestic-relations law requiring premarital examinations have been issued by the State Commissioner of Health of New York. No marriage license shall be issued to any person unless he or she shall submit a statement on forms provided, signed by a licensed physician and by the director of an approved laboratory, that the applicant has been examined and is free from syphilis in a stage which may become communicable. An order dispensing with such requirements may be issued by a justice of the supreme court or the county judge, or the judge of the children's court when the woman is between 14 and 16 years of age. No proof of freedom from syphilis shall be required if the woman is pregnant.

A duly licensed physician is one licensed under the laws of New York State, or a commissioned medical officer of the United States Army, Navy, or Public Health Service. A list of approved laboratories will be supplied to physicians and clerks, with revision from time to time.

The examination shall have been made not more than thirty days prior to that on which the license is applied for.

The physician's and laboratory's statement, or court order which provides for a waiver, shall be forwarded to the State department of health when the completed marriage records are sent.

Biological aspects of sex. Oscar F. Cox. Boston, 1939 (Mimeographed).

This is one of the lectures on social hygiene given for social-group leaders at

the Boston City Hospital, 1939, under the auspices of the Boston City Hospital and the Massachusetts Society for Social Hygiene. The author discusses the anatomy and functions of both male and female sex organs and emphasizes the need for wider dissemination of information about sex.

Most persons receive no training in sexual matters until they suddenly become aware of the desire, then the training is usually little more than the admonition, "Do not touch!" It is little wonder that many young people make such serious mistakes. Sex training is part of character development. If children had no training in honesty early in life, how many would resist the temptation to be dishonest? Yet boys and girls are expected to curb the powerful instinct of sex without an adequate understanding of its proper and improper use.

A person who is sexually promiscuous experiences a form of transitory pleasure, but never achieves real happiness. Such happiness follows mastery of the sexual life and the use of sex in the only way that will work satisfactorily in this complex civilization. History has demonstrated that promiscuity in sexual matters is unworkable in any kind of a social order.

Preparing children for the awakening of sexual desire, teaching them the dangers of its misuse, keeping their minds and bodies occupied in interesting and valuable pursuits, and directing them toward the appreciation of true values will be instrumental in improving the present situation. The large number of extramarital pregnancies and the millions of American youngsters infected each year with gonorrhea and syphilis would seem to be ample reason for action to correct the condition.

Venereal diseases and the general practitioner. L. W. Harrison. Practitioner, London. Aug. 1939, 143: 129.

While many practitioners are apt to think that venereal diseases are outside their province, records of clinics and of specialists show that sound knowledge possessed by the practitioner of the re-

quirements for diagnosis and treatment in a patient with venereal disease has often affected profoundly the future development of the infection. Specialists often regret the opportunities for effective intervention which practitioners have missed. The combined efforts of practitioners and treatment centers have brought about an encouraging reduction in the incidence of fresh syphilis in Great Britain, which is probably not more than one-fourth of what it was in 1920. The great increase of early syphilis during the years 1914-1918 would justify a corresponding increase now in mortality from such late manifestations as general paresis, tabes dorsalis and aneurysm, and a comparison of the death rates from 1920 to 1937 are interesting. The rate per 1,000,000 population for general paralysis in 1920 was 66 for males and 12 for females; in 1937 this rate was 30 and 12, respectively, which probably means that the men were brought under treatment more promptly than the women. For aneurysm, however, the rate for females increased from 9 in 1920 to 25 in 1937 and for males from 44 to 51, showing that antisypilitic measures are not so effectual after the vascular defect has been diagnosed.

It is of great importance that more practitioners realize the invaluable aid of microscopic examination in the diagnosis of primary syphilis. Due to the milder reaction of female tissues to the *S. pallida* and to the lack of awareness of syphilis on the part of medical attendants, the proportion of infections in women which escape detection and treatment is much too high. General practitioners could do an immense amount of good by promoting and encouraging the greater use of the blood test in women, but always with the proviso that a positive reaction is not to be accepted as conclusive evidence of syphilis unless backed by other evidence.

The development of the sulfonamide treatment in gonorrhea promises eventually as great reductions in the incidence of that disease as modern treatment has brought about in syphilis.

But there is danger of a temporary increase in incidence due to inadequate dosage and the lack of strict tests of cure, which leaves many symptomless carriers to spread the infection. General practitioners should make more use of their privilege of consulting with medical officers at treatment centers to learn first hand the latest developments in methods of treatment rather than depending upon publications.

LABORATORY RESEARCH

The effect of sulphanilamide upon spermatogenesis in man. Norris J. Heckel and C. G. Hori. *Am. J. M. Sc., Philadelphia.* Sept. 1939, 198: 347.

The authors report the results of a study to determine whether the administration of sulfanilamide derivatives to man influences spermatogenesis. The semen from 11 patients was analyzed before and after sulfanilamide was given. In contrast to reports of other investigators, there were no noteworthy effects upon the total number or percentage of live spermatozoa from the use of sulfanilamide in these patients. Variations in the total spermatozoa counts shown during and after treatment were no greater than the variations which occurred before the drug was given. A table is presented giving in detail the results of the study.

Studies on the mode of action of sulfonamide compounds in streptococcus and inguinal lymphogranuloma infections in mice. H. Schlossberger and F. Bar. *Zentralbl. f. Bakt., Jena.* Aug. 1939, 144: 228.

On the basis of experiments in mice the authors report that the therapeutic effect of prontosil derivatives in streptococcus and venereal lymphogranuloma infections is only a transitory inhibition of the activity of the causative agent

and does not represent actual cure of the disease. Mice which were inoculated with the brains of other mice which had been apparently cured by means of protosil derivatives, nevertheless developed venereal lymphogranuloma infections. The infection was, however, not sufficiently severe to result in death in any of these animals. The authors assume that the sulfonamides have an inhibitive action on the bacteria but that the resistance of the body to the infection determines whether actual cure will take place.

Determination of sulfanilamide in tissue, urine and blood. A modification of Marshall's method. Frank T. Maher and W. J. R. Camp. *J. Lab. & Clin. Med.*, St. Louis. Aug. 1939, 24: 1198.

In a study of the distribution of sulfanilamide in the body two difficulties were met in using Marshall's original method for the determination of the drug: (1) A brown interfering color developed, and (2) quantitative recovery of the drug added to tissue and fluid samples before extraction was not always possible. A modification of Marshall's method for the determination of sulfanilamide in tissue, urine, and blood is given in which silver nitrate is used to remove interfering substances, notably chloride. An excess of silver nitrate does not interfere with the determination. The fact that the addition of chlorides to a sulfanilamide solution intensifies the interfering color while the use of silver nitrate removes it, indicates that the chlorides present in the material are responsible in large part for the difficulties encountered. Apparently the silver nitrate removes other substances, as judged from the muddy brown precipitate. In the determinations made upon blood samples, it was noted that 1 cc. of silver nitrate solution was not sufficient to remove all the interference, although that quantity had been sufficient for the samples from tissue and urine. Increasing the quantity of silver nitrate to 2 cc. effectively removed all interferences.

Epinephrine, ephedrine, quinidine and other amino compounds were found to interfere with this test.

Clinical and experimental study of interstitial keratitis. Joseph V. Klauder. *J. Investigative Dermat.*, Baltimore. Aug. 1939, 2: 157.

Explanation of certain features of interstitial keratitis are lacking, and Klauder discusses the study of some of the pertinent problems. *Spirochaeta pallida* were not found in pieces of cornea removed from patients with interstitial keratitis when they were examined by different methods. Rabbits were injected intraocularly with horse serum. The ocular response to second injections of horse serum was studied by slit lamp microscopy and no definite evidence of an allergic reaction was found. Cutaneous tests were performed on patients with interstitial keratitis, using a piece of cornea of the same patient and also the cornea of a syphilitic fetus. These tests were negative. It was not possible to produce interstitial keratitis in syphilitic rabbits by repeatedly traumatizing the cornea.

Studies were made of heat applied to the cornea in treatment of the disease. The experiments showed that the cornea is a poor conductor of heat and it is not possible, after employing the thermophore in treatment, to conclude by deduction that *Spirochaeta pallida* are not present in the cornea.

Study of the absorption of neoarsphenamine by the cornea after instillation into the conjunctival sac showed that no arsenic was present in the cornea. Following 6 consecutive daily intravenous injections of neoarsphenamine (30 mg. per kg. of body weight), arsenic (0.04 mg.) was present in each cornea. Repeated instillation of a 1:600 dilution of neoarsphenamine (the solution being maintained in the sac at each instillation for 20 minutes), did not influence the course of the disease.

Klauder says that there is no satisfactory explanation of what determines the onset of interstitial keratitis first in one eye and later in the second eye. The

allergic concept does not explain the onset predominantly between the ages of 8 and 15 years, the recurrence of the disease in the same eye, nor its occurrence after trauma; there are fewer objections to the theory that the disease is caused by the presence of *Spirochaeta pallida*. Interstitial keratitis is peculiarly a manifestation of congenital syphilis, along with Hutchinson's teeth and the facies of congenital syphilis. The onset of the disease after thorough antisyphilitic treatment is unique in the domain of syphilis, and this gives rise to the question whether the disease is entirely a syphilitic process. The presence of arsenic in the corneas of rabbits treated with neoarsphenamine, as shown in this study, does not support the assumption that the poor response to antisyphilitic treatment is due to the fact that the cornea is an avascular organ not easily accessible to antisyphilitic drugs.

Sulphanilamide chemotherapy. (Discussion at the scientific meetings of the British Medical Association, July 26-28, 1939.) *Lancet*, London. Aug. 12, 1939, 2: 371.

C. H. Browning stated that in experimentally produced streptococcal infections in mice, individuality seemed to be a prominent feature of responses to treatment with sulfanilamide drugs; a relatively small dose might cure one mouse whereas much larger doses might fail in others. The drugs were relatively inefficient in the treatment of localized infections of some duration. The properties of these drugs demonstrable *in vitro* did not explain their therapeutic effect and did not supply data for assessing their curative action. It is likely that the body, while under the influence of the drug, behaved toward highly virulent organisms much as the normal animal did to nonpathogenic types, which were slowly destroyed.

G. A. H. Buttle divided the derivatives of sulfanilamide into two groups—those with substituents in the amino group and those with substituents in the amide group. In the first group were prontosil rubrum, prontosil soluble, rubiazol, pro-

septasine, and soluseptasine. The activity of these compounds was probably due to their break-down within the body into sulfanilamide. These drugs had no advantage over sulfanilamide in infections in which they were therapeutically effective. Although some were less toxic they were also less active than sulfanilamide. In the second group were uleron, albucid, and M & B 693. These drugs did not break down into sulfanilamide in the body but were themselves the active agents against the bacteria. M & B 693 is more effective than sulfanilamide in gonococcal infections. Uleron tends to produce peripheral neuritis and does not seem to be any more effective in gonorrhea than sulfanilamide. Albucid, which seems to be completely nontoxic, is effective in gonorrhea, especially in females. A concentration of sulfanilamide in the blood of 10 mg. per 100 cc. is required for treatment of severe infections. Agranulocytosis is the only fatal complication produced by these drugs. Cyanosis is a common toxic symptom, but this should not be regarded as a sign of overdosage. Occasional hematuria is due to the deposition of the acetyl derivative in the renal tract. Vomiting and mental depression are more common with M & B 693 than with sulfanilamide.

F. J. T. Bowie stated that sulfanilamide treatment for gonorrhea has resulted in cures in 70 to 80 percent of cases, uleron in 70 to 90 percent, and M & B 693 in 85 to 95 percent. M & B 693 seems to be the drug of choice since it can be given at once, whereas optimal results with sulfanilamide and uleron are obtained only if treatment is postponed for about 10 days from the onset of the disease. After treatment with M & B 693, complications of gonorrhea developed in only 1.5 percent of the patients compared with 25 to 30 percent before the advent of chemotherapy. A total of 20 gm. of M & B 693 was usually sufficient for cure. This could be given in daily 3-gm. doses for 6 or 7 days; or 4 gm. could be given at one time, then 2 gm. 4 hours later, followed by 1 gm. 4 times a day until the total

amount reached 20 gm. When the latter method was used, nausea lasting 12 to 24 hours was common, but there seemed to be no danger and the results of treatment were better. In a series of 7 cases of gonococcal ophthalmia neonatorum treated with M & B 693 all patients became bacteriologically negative within 36 hours; confinement to the hospital was reduced to about 7 days compared with much longer periods needed for older methods of treatment.

Acetyl derivative of sulphanilamide.

Brit. M. J., London. Aug. 12, 1939, 2: 339.

Albucid is an acetyl derivative of sulfanilamide, namely, p-aminobenzenesulfonacetamide. Sulfanilamide is partly detoxicated by acetylation in the human body, the p-amino group being acetylated to form a product which is therapeutically inactive. In albucid the amino group in the sulfonic acid side chain is acetylated, and the compound has a high therapeutic activity. The special advantages claimed for this compound are that it is rapidly absorbed and excreted and that it is excreted in an unaltered form. These properties cause the drug to have an extremely low toxicity.

The drug is reported to be effective and nontoxic in gonorrhea. The initial dosage suggested is 4.5 gm. per day.

PATHOLOGY

The myogram in tabes dorsalis and general paresis. H. Kramer and G. Schaltenbrand. *Deutsche Ztschr. f. Nervenhe.*, Berlin. Aug. 1939, 149: 117.

The authors state that myographic studies were made on 20 patients with tabes dorsalis, general paresis, and taboparesis. The results obtained on 2 patients with tabes dorsalis, 3 with general paresis, and 2 with taboparesis are reported in detail. Some of the tabetics who had lost all of the leg reflexes still had normal myograms and only some of

them had the muscular hypotonia which they would be expected to have. Some also showed a shift of balance to the extensor side. The majority of patients with general paresis and taboparesis had myograms which revealed slight rigidity or definite spasticity.

In comparing the spastic manifestations of general paresis with the psychic and serologic findings, it was observed that only 2 patients with general paresis did not have increased myotatic reflexes. Only 1 of the tabetics had a slight rigor. Three of the taboparetics and 6 of 9 tabetics had a definite hypotonia. One patient with cervical tabes had a mixture of rigor and hypotonia. Periodic variations were observed in 3 of the 8 taboparetics and in 3 of the 9 tabetics. Relaxation is very incomplete in general paresis.

It is pointed out that by means of the myogram it is possible to differentiate between tabes and taboparesis in doubtful cases in which the serologic findings are not available.

The pathogenesis of the Wassermann reaction in the cerebrospinal fluid.

H. Demme. *Deutsche Ztschr. f. Nervenhe.*, Berlin. Aug. 1939, 149: 169.

The case of a 56-year-old man with classical symptoms of tabes dorsalis is reported. The blood Wassermann reaction was negative while that of the spinal fluid was strongly positive. The spinal fluid furthermore showed a marked increase in protein content, normal appearance, normal cell count, and normal rise with the Queckenstedt procedure. After several days a transverse paralysis extending up to the sixth thoracic segment developed very rapidly. The spinal fluid obtained by cisternal puncture showed only slight nonspecific changes with a negative Wassermann reaction. The lumbar spinal fluid showed a typical compression syndrome with a strongly positive Wassermann reaction. The presence of tumor metastases in the spine was suspected but no primary tumor could be detected on careful clinical examination. The patient died of hypostatic pneumonia and ascending

pyelitis 12 days after admission to the hospital. At autopsy metastatic carcinoma of the spinal cord and a very small primary carcinoma of the prostate gland were found.

In explaining the findings in this case, the author discards the possibility of a falsely positive Wassermann reaction on the basis of findings in the same hospital on a number of other cases of tumor of the spinal cord. He presents two possible explanations. First, that Wassermann reagins have passed from the serum into the blocked-off portion of the spinal fluid. Second, the formation of reagin in the central nervous system itself (intramural origin). The first possibility is unlikely since the blood Wassermann reaction was repeatedly negative. The author accepts the second explanation as being more likely.

Aneurysm of the aortic arch. A. Leger and A. de Guise. *Union méd. du Canada*, Montreal. Aug. 1939, 68: 836.

The authors report the case of a 65-year-old woman with a perforating aneurysm of the aortic arch. The perforation existed for 5 years before the patient died. Hematomas would occur at the site of the pulsating sternal tumor and then would be resorbed. It was thought that antisyphilitic treatment given over a period of 3 years prevented the sudden rupture of the aneurysm.

Encephalomyelitis following administration of sulphanilamide. J. H. Fisher and J. R. Gilmour. *Lancet*, London. Aug. 5, 1939, 2: 301. (Editorial comment on page 325.)

The authors describe two cases of encephalomyelitis following the administration of sulfanilamide. One of the patients died. The total doses were small (14 and 18 gm.), and if the drug was responsible the patients must have been more than ordinarily susceptible to it.

In one case (treated for lupus erythematosus) the symptoms suggested an acute ascending myelitis, and the outstanding post-mortem features were per-

ivascular demyelination of the spinal cord in the thoracic region, vascular damage, and massive softening of the spinal cord in the lumbar region. In the second case (treated for tonsillitis, cervical adenitis, and erythema nodosum) the clinical findings were consistent with encephalomyelitis.

Very few affections of the central nervous system attributable to sulfanilamide have been reported. Several cases of neuritis have been described following treatment with uleron.

The toxic manifestations which some persons have after taking small amounts of some drugs are not usually those seen in cases of overdosage of the drugs. The cause of the idiosyncrasy is not known. Occasionally the symptoms appear after the first dose, and there seems to be a constitutional factor involved. Often, however, they come on only after a number of doses, and in these cases there seems to be a definite sensitization to the drug. Once patients become sensitized, a minute dose of the drug will bring on a recurrence of the symptoms. It is possible that encephalomyelitis developing during treatment with sulfanilamide or with arsenical drugs is the result of such a reaction affecting the central nervous system.

Laryngeal vertigo occurring in a case of aneurysm of the aorta. P. J. Molloy. *Brit. M. J.*, London. Aug. 12, 1939, 2: 335.

The case is reported of a man, aged 56, with a positive blood Wassermann test, an enlarged heart, and an aneurysm of the ascending aorta, who had recurrent brief attacks of unconsciousness after coughing. On each occasion he first experienced a tickling in the throat followed by severe coughing and a choking sensation, then he felt slightly giddy and finally fell backward losing consciousness. The periods of unconsciousness lasted one or two minutes, and there were no involuntary movements of any part of the body either before or during the attacks.

While the patient was given treatment in a hospital for a period of 2

months he had no attacks of unconsciousness, although he had several during a month period following discharge from the hospital. He finally abandoned treatment and contact with him was lost.

Incidence of eye and nervous system involvement, of aortitis and of leukoplakia in patients treated for syphilis in the dispensary of Nice. Boisseau, Spinetta, Druelle and Durandy. *Prophylax. antivén.*, Paris. Aug. 1939, 11: 501.

Among 1,026 patients (607 men and 419 women) treated for syphilis and followed by means of clinical and neurologic examinations after treatment had been stopped, 12 (4 men and 8 women) were found to have developed tabes. Two of the tabetics had not received treatment for 2 and 10 years respectively, after having each had 2 years of treatment. The 10 other tabetics were still receiving treatment for various types of syphilis other than central nervous system syphilis. However, 76 (7.4 percent) of the patients in the entire group had some pupillary abnormality. Altogether 23 (2.2 percent) of the 1,026 patients had manifestations of central nervous system involvement of one kind or another; whereas, in a group of 668 prostitutes who were studied in the same way and among whom 307 (46 percent) were definitely syphilitic, only 3 (1 percent) had any central nervous system involvement and these had only pupillary changes.

The entire group was not studied serologically so that no definite statement is made regarding the incidence of syphilitic heart involvement.

Leukoplakia was found in two women who smoked a great deal. None of the 307 prostitutes with syphilis had leukoplakia, although many of them were smokers.

The authors conclude, in view of the fact that tabes developed in patients under observation and in the presence of continuously negative serologic reactions, that the serologic tests are not sensitive enough to detect an infection apparently still active.

Puerperal agranulocytosis following sulphanilamide treatment. Record of a fatal case. I. Kenworthy Gayus, V. B. Green-Armytage and J. K. Baker. *Brit. M. J.*, London. Sept. 9, 1939, 2: 560.

A woman (age 24 years) with a hemolytic streptococcal infection following childbirth was given the following treatment with prontosil album and sulfanilamide (a total of 39½ gm. over a period of 17 days): June 11 and 12, 1939, a total for the 2 days of 3 gm. of prontosil album; June 13, one gm. only; June 14, 6 gm. sulfanilamide; June 15, 4 gm. of the latter drug; June 16, 3 gm.; the dosage was gradually lessened on the following days because of a reduction in severity of symptoms; on June 25 and 26, after an increase of fever, 3 gm. of sulfanilamide was given each day; June 27, 2 gm. On June 28 the patient became very ill, had a high fever with symptoms of agranulocytic angina, the hemoglobin was 67 percent and the leukocyte count was 850 per cubic millimeter (lymphocytes, 90 percent; monocytes, 10 percent; no polymorphonuclears seen).

As soon as the diagnosis of agranulocytosis was confirmed, 20 cc. of pent-nucleotide was given intramuscularly and 1,100 cc. of citrated blood was given by Marriott's continuous-drip blood transfusion method during the next 13 hours. At the end of the transfusion the leukocyte count had fallen to 680 per cubic millimeter, the differential percentages remaining the same. A total of 100 cc. of pentnucleotide was administered within 38 hours, but the patient's temperature mounted to 105.6° (axilla) and she died. Post-mortem examination revealed congested appearance of the heart, lung, spleen, and liver. The faucial pillars, tonsils, and hypopharynx had a sloughing gangrenous form of inflammation. It was stated that "the circumstances in this case afford strong presumptive evidence that the agranulocytosis was due to sulfanilamide. This type of disease did not occur with streptococcal puerperal infections until treatment with this group of drugs (sulfanilamides) came into use."

It is urged that complete blood counts be made in all cases in which the patient is given more than 25 gm. of the drugs.

Congenital syphilis and its effect upon eyesight. Philip S. Luedde. J. Missouri M. A., St. Louis, Sept. 1939, 36: 371.

Ocular manifestations of congenital syphilis include rhagades at the angle of the lids and blepharitis characterized by small discrete ulcerations accompanied by an absence or loss of eyesight, chronic periostitis involving the orbit, external muscle palsies, interstitial keratitis, involvement of the uveal tract (usually associated with interstitial keratitis) resulting in posterior synechiae from iridocyclitis and anterior choroiditis, optic atrophy occurring secondarily as a result of neuritic inflammation.

Treatment consists of local measures (cycloplegia with atropine, relief of photophobia by protection against light, and care of complications as they arise) and adequate, prolonged antisyphilitic treatment. Prophylaxis may be carried out by complete examination of pregnant women (including serologic tests in all cases) and prolonged antisyphilitic treatment for all found to have the disease. Early and adequate antisyphilitic treatment of children with congenital syphilis will prevent many of the painful and destructive ocular manifestations of the disease.

The toxic effects of sulfanilamide and sulfapyridine. Clyde Brooks. New Orleans M. & S. J. Sept. 1939, 92: 115.

The history and therapeutic benefits of sulfanilamide and sulfapyridine are briefly discussed, and the toxic effects of the drugs are described in detail. Cyanosis is a frequent effect which may be caused by the formation of methemoglobin, sulfhemoglobin, or by a black oxidation product of the drugs which dyes the red corpuscles. Five percent methemoglobinemia will produce clinical cyanosis, and 15 percent produces profound cyanosis. Stopping the drug usually results in a disappearance of the cyanosis

in about 24 hours, and the administration of one or two grains of methylene blue in capsules every 4 or 5 hours accelerates the disappearance of the reaction. For sulfhemoglobinemia, methylene blue has no appreciable effect, but the use of oxygen is beneficial. Ultraviolet radiation seems to produce a purplish color in the drugs, and this may cause apparent cyanosis in the patients.

If hemolytic anemia develops as a result of treatment, the drug should be discontinued immediately, fluids forced, and transfusions given. Hemolytic jaundice and granulocytopenia are other serious reactions to treatment. Skin reactions include purpura, erythema scarlatina, exfoliative dermatitis, allergic sensitization, and photosensitization (eruptions appearing only on the areas exposed to sunlight). McGinty, Lewis and Holtzclaw have reported that some of the mild toxic symptoms can be relieved by the use of nicotinic acid in 50 mg. doses 3 times a day.

The author suggests that sulfanilamide and sulfapyridine be used only in cases of infection in which the outlook is not good. If the outlook is good, the danger of their use may exceed the risk of infection. To use sulfanilamide and sulfapyridine freely and indiscriminately may result in severe, dangerous poisoning, and may sometimes cause a fatality.

Hypersensitiveness to light caused by uliron. G. Grave. Med. Klin., Berlin Aug. 11, 1939, 35: 1078.

A case is reported in a man of 25 who was given uliron for gonorrhea. The dosage was 3 half-gram tablets a day. A total of 49 tablets was given from March 26 to April 16. On April 16 while he was still taking daily doses of uliron his face became red and began to swell. There was intense itching and burning. The swelling progressed until his eyes were swollen shut. The hands also were greatly swollen. After his recovery from this attack the patient took uliron again without a physician's prescription and had a second severe attack of the dermatitis. Later doses of uliron were given experimentally

Whenever the administration of the drug was followed by exposure to sunlight the dermatitis recurred. When hands or face were protected from the sunlight they did not swell but only the parts exposed to sunlight were affected. On several occasions the patient was exposed to strong sunlight when he had not taken uliron and no dermatitis developed.

Urobilin and an increase of urobilinogen were found in the urine while the patient was taking uliron daily which suggested that the dermatitis might be caused by injury of the liver, but treatment with liver extract or with detoxifying vitamin C and insulin therapy neither prevented the attacks when uliron was given nor hastened their cure. The fact that the patient remained sensitive to small doses of uliron long after the regular administration of the drug had been stopped indicated a delayed excretion of the drug. A severe, almost urticarial dermatographism indicated a certain degree of nonspecific sensitiveness of the capillaries but as this was not tested until late in the course of the condition it may have been due to injury by the sulfanilamide.

Whatever the mechanism of action, the case illustrates the danger of long-continued uliron therapy and the author believes that a series of treatments should not last more than 4 days and that no more than 24 tablets should be given. After an interval of not less than 10 days another series may be given and his process may be repeated for as many as 4 series.

DIAGNOSIS

Serological reactions in kala-azar: complement fixation, false Wassermann reaction, and high anti-complementary titre. S. D. S. Greval, P. C. Sen Gupta and L. Everard Napier. *Indian J. M. Research*, Calcutta. July 1939, 27: 181.

The authors present a detailed description of the complement fixation test for kala-azar, using the Witebsky, Klinge-

stein and Kuhn (W. K. K.) antigen. They describe 5 cases of patients with kala-azar whose Wassermann reactions for syphilis were falsely positive, and they discuss the high anticomplementary titer of serum in this disease.

Among 40 patients with kala-azar 4 had false positive Wassermann reactions, 3 had true positive reactions, 15 had doubtful (false) reactions, 5 had anticomplementary serums, and 13 had negative reactions. The positive, doubtful, and anticomplementary rates of this group are much higher than the rate for an unselected hospital population given previously by Greval, Sen Gupta and Das.

Roentgen examination of the aorta and pulmonary artery. Marcy L. Sussman. *Am. J. Roentgenol.*, Springfield. July 1939, 42: 78.

Well-defined deviations from the normal in the size of the aorta yield evidence of disease. Experience in roentgenoscopy of the chest, particularly as it permits observation of the variations in the great vessels due to the position of the diaphragm, of posture, of chest deformity, and of age has appeared more valuable than rigid application of mensuration. The smaller the deviation from normal the less valuable and sometimes more confusing is the information obtained.

Sussman says the roentgen examination of the aorta may not prove particularly valuable in the diagnosis of syphilitic aortitis. Some authorities have claimed that early syphilitic aortitis is associated with localized pulsations of the ascending aorta, but Sussman has not been able to confirm the observation in his small series. Kymographic studies on cases of syphilitic aortitis have given the impression that the coronary ostia will be narrowed in many cases before the evidence of aortitis is clear.

Aortic aneurysm may be diffuse or sacculated. The diagnosis is made by the demonstration of a dilated segment of the aorta or the demonstration of a mass which is part of the aorta. Careful roentgenoscopy is the only satisfactory method of diagnosis. Theoretically, when the aneurysm is not part of the

ascending aorta it should be possible to demonstrate syphilitic aortitis in this segment of the aorta, but this cannot always be done. When the aneurysm is of arteriosclerotic origin the other portions of the aorta show the tortuosity and dilation expected in this condition. In the absence of aortic insufficiency, the heart in syphilis is usually not enlarged.

Ayerza's disease is a sclerosis of the pulmonary artery previously thought to be regularly syphilitic but which now is considered not necessarily specific. There are roentgenologic signs of emphysema, and tracts corresponding to the ramifications of the pulmonary artery are seen extending through the entire pulmonary area out to the periphery.

Sussman says it is his impression that, regarding the two great vessels, if the roentgenologic findings are considered alone and completely apart from the clinical data, the value of the examination has been overestimated in the literature. In actual practice it has its definite place when considered as an integral part of the physical examination.

The value of roentgenographic examination in the diagnosis of syphilis in newborn infants. Amos U. Christie. *J. Pediat.*, St. Louis. Aug. 1939, 15: 230.

The author reports on a study which was made of 83 infants who were born of syphilitic mothers. Each of the infants was followed clinically and serologically until he was considered to be proved syphilitic or nonsyphilitic. Of the roentgenographic examinations of the long bones made within 10 days of birth, 57 were recorded as negative for syphilis, 3 as positive, and 23 as doubtful. Of the 57 recorded as negative 10 were subsequently considered syphilitic; of the 3 with positive roentgenographic diagnosis, evidence of syphilis developed in 2, and of the 23 doubtful cases, 3 were afterward diagnosed as syphilitic. Therefore, in only 2 cases was the roentgenographic examination of value in establishing an early diagnosis of syphilis, and in 49 cases a correct diagnosis was made by this examination.

Submetaphyseal rarefaction and coracal shadows seen in the roentgenogram may be due to conditions other than syphilis; both conditions may occur in normal, rapidly growing infants. Caffo has shown that treatment of pregnant women with bismuth brings about changes in the bones of fetuses, described by him as "heavy transverse bands of increased density at the ends of shafts." Of the 83 infants studied there were 73 whose mothers had been given bismuth injections during pregnancy, and in 22 of these cases a diagnosis of doubtful syphilis was made by roentgenogram. In the 10 cases in which the mothers had not been given any treatment with bismuth, there was only one in whom doubtful syphilis was diagnosed. Christie believes that it is advisable to confirm roentgenographic findings by clinical or serologic examination before a definite diagnosis of syphilis is made and treatment is instituted.

Determination of cure of venereal diseases. H. Fuhs. *Wien. klin. Wchnschr.* Berlin. Aug. 11, 1939, 52: 745.

The author outlines the criteria of cure for venereal diseases. He states that for chancroid a period of observation of 3 months is all that is required. During this interval blood tests for syphilis can be made every 1 to 4 weeks to rule out concomitant syphilitic infection. Infectiousness of syphilis depends on the age of the infection, the amount and character of antisyphilitic treatment and the length of the period of observation during which clinical, roentgenologic and serologic examinations are made. After a period of observation arsphenamine provocation is advised. In case of old infections blood tests following provocations should be continued for 5 to 6 weeks. The accepted criterion of cure is an interval of 4 years since the time of infection including a period of observation of 2 years during which all examinations for syphilis are negative. In case of seronegative primary syphilis this interval is shortened to 2 years with a 1-year period of observation, provided that treatment with neoarsphenamine

and bismuth has been intensive and adequate in amount. Women who have or have had a syphilitic infection should be treated during each pregnancy. Wassermann-fast patients should be examined for possible syphilitic manifestations at regular intervals. For cases in which the time of infection cannot be determined, it is best to date the infection from the time when the disease was first recognized. There is no contraindication to the marriage of persons with congenital syphilis, provided that the spinal fluid is normal. Congenitally syphilitic women should, however, be treated during pregnancy.

Gonorrhea is considered cured in men and women if the tests for cure are negative for 3 months after treatment has been discontinued and in female children for 4 months of observation. At least 3 examinations should be made following provocation.

Negative serologic reaction for syphilis in nine patients with infectious mononucleosis. John H. Mills and Elsa Jahn. *J. Lab. & Clin. Med.*, St. Louis. July 1939, 24: 1076.

Bernstein and Hatz have each reported positive blood tests for syphilis in patients with infectious mononucleosis. The writers report on 9 patients at the Johns Hopkins University Hospital who had a diagnosis of infectious mononucleosis. In 5 of these patients the technic of Bernstein was used, and in 4 the rapid method of Straus was used in addition to the Bernstein modification of the Paul-Bunnell test. The Kolmer complement fixation test and a flocculation test were negative in every instance. While chance may account for the discrepancy between these results and those of Bernstein and Hatz, the authors desire that these cases be added to the literature.

Conflicting serologic tests for syphilis using multiple standard tests in parallel. A critical study based on adequate clinical control. Arthur G. Schoch. *Urol. & Cutan. Rev.*, St. Louis. July 1939, 43: 463.

The evaluation of questionable or conflicting positive and negative serologic

reports for syphilis is rapidly assuming major proportions. The reasons are two-fold: First, because modern serologic laboratories are now required, for the sake of efficiency, to do routinely two or more standard tests; and, secondly, because routine tests on apparently normal persons, in the form of the serologic dragnet, are becoming very popular.

Until a perfect test for syphilis is devised (at present there is none) each patient with a questionable serologic report will have to be evaluated, after taking into consideration the history, physical examination, and the spinal fluid examination, by capable syphilologists who have more than a casual knowledge of the variable factors affecting their own laboratory.

Any one who has had extensive experience in the laboratory diagnosis of syphilis is fully aware of the number of factors which influence the sensitivity and reliability of serologic tests. The seasonal change in the complement titer of guinea pig serum, the variability in sheep cell hemolizing quality, and the variation in sensitivity of new batches of antigen for the flocculation tests, are a few of the factors.

During the last 12 months 3,000 new patients have been examined in the clinics with which the author is associated, 95,000 treatments have been administered and 6,000 blood serums have been tested using the Kolmer-Wassermann, the Kahn and the Kline flocculation tests in parallel. In addition the Eagle complement fixation and flocculation tests are included in the investigation of questionable cases. With respect to the relative sensitivity of the 5 tests employed, Schoch says they have found the Kolmer-Wassermann to be the least sensitive. The Kahn and the Eagle complement fixation tests are approximately equal in sensitivity; the Kline and the Eagle flocculation tests are the most sensitive, and they yield the greatest number of false positive results.

Schoch feels that conservatively he may say no individual test is adequate for the diagnosis of syphilis. By doing

2 or 3 tests in parallel the diagnostic efficiency of blood serologic tests can be raised from a general level of about 75 percent efficiency to one which probably exceeds 90 percent efficiency. The serologic tests for 26 percent of 3,000 patients under treatment for syphilis yielded conflicting results; only 25 percent of the 3,000 blood serums were positive when 3 standard tests were used.

TREATMENT

The treatment of early syphilis. Robert Lees. Practitioner, London. Aug. 1939, 143: 134.

Lees feels convinced that, apart from the laboratory methods required for diagnosis, the treatment of early syphilis is within the province of most practitioners. In the early diagnosis of suspected cases the blood should be examined by the Wassermann or the Kahn test, or both, and serum from the chancre by dark-field examination. If these tests are negative, the blood should be examined every 2 weeks until 14 weeks have elapsed since the exposure to infection. The earlier the diagnosis the better the prognosis. Local treatment of the chancre is relatively unimportant. Treatment must be intensive at the outset to control contagious lesions; then less intensive dosage must be continued for not less than one year. Adequate amounts of arsphenamine and bismuth must be given and there should not be prolonged intervals without treatment.

After treatment is finished, clinical and serologic observation should continue for 2 years; this implies recognition of the importance of the disease by both the patient and the doctor and full cooperation and attention to details. In a review of 300 cases of early syphilis Lees found that 40 percent were inadequately treated according to standards advocated by the League of Nations Committee or the American Cooperative Clinical Group. This is largely because hospital

patients discontinue treatment when still uncured, and, to a lesser degree, because some practitioners reduce the dosage to such an extent that permanent cure is improbable. A negative Wassermann is not proof of cure or even of inactivity of syphilis. The toxic effects of anti-syphilitic treatment are not serious if a careful watch is maintained for the early signs.

Lees believes that it is important not to minimize the importance of the disease but to give a confident assurance of ultimate cure, enlisting the cooperation of the patient.

Treatment of induced malaria in Negro paretics with mapharsen and tryparsamide. Martin D. Young and Sol B. McLendon. Pub. Health Rep., Washington. Aug. 18, 1939, 54: 1511.

Mapharsen, recently reported to be effective against tertian malaria (*P. vivax*), was tried against quartan malaria (*P. malariae*). Ten Negro paretics in whom malaria was used in antisyphilitic treatment were given mapharsen. Two of the patients were also given a course of tryparsamide. These patients still had parasites in blood smears 22 weeks after completion of the mapharsen treatment. Subinoculations from 2 of the mapharsen-treated paretics resulted in typical malaria infections, thus proving that the parasites were viable.

In 11 Negro paretics, tryparsamide was used against *P. malariae*. The parasites never disappeared from the blood. A subinoculation from the tryparsamide-treated group produced an infection, proving that the parasites were viable.

As these drugs relieved the symptoms without eradicating the infection, the authors pointed out that their use might inadvertently result in the release of carriers of quartan malaria, thus establishing foci of infections of a type of malaria now rare in the United States.

Sulfonamide and spermiogenesis. Günter Greulich. Arch. f. Dermat. u. Syph., Berlin. June 29, 1939, 179: 2.

There have been a considerable number of articles published which hold that

permatogenesis is lessened by the use of the sulfonamide and related compounds which are now being given so freely in gonorrhea and various other infections. The author made a systematic quantitative and qualitative examination of the semen after the administration of these drugs in 40 cases of gonorrhea.

In 31 of the cases the drugs were found to have no effect on the production of spermatozoa. In 9 cases oligospermia, hypospermia, or azoospermia was found, but there was evidence to indicate that these conditions were caused by the complicated gonorrhea rather than by the drugs.

Chemical analyses showed that the sulfonamide was excreted through the ejaculate, the amount of excretion sometimes being greater than the blood content of the drug, but this did not cause any decrease in the number of spermatozoa in the ejaculate.

The author concludes that the drugs of the sulfonamide series do not in any way affect spermiogenesis or injure the organs that produce spermatozoa.

Granulocytopenia in sulfapyridine therapy. Vera B. Dolgopel and Harold M. Hobart. J. A. M. A., Chicago. Sept. 9, 1939, 113: 1012.

The authors reviewed the recent literature and found that three cases of granulocytopenia and a number of cases of leukopenia were observed in the course of sulfapyridine therapy. The authors added to the number two cases of granulocytopenia and two cases of definite leukopenia. One case of granulocytopenia, complicated by a mild aplastic anemia, was fatal. In at least two cases of granulocytopenia sulfapyridine was apparently the only cause of the condition. In the other three cases a coincident damage to the bone marrow by the original infection or by a previous infection might be considered a contributory factor in the development of granulocytopenia. In two cases the condition developed after the discontinuance of the sulfapyridine therapy.

The conclusion is reached by the authors that a high total intake of sulfapyri-

dine may cause granulocytopenia. The damage to the bone marrow consists in depression of maturation of myeloid cells. Erythropoiesis may also be occasionally disturbed. Blood counts should be made twice a week during sulfapyridine therapy and continued for two weeks after withdrawal of the drug.

Prescriptions for sulfanilamide. Lancet, London. Sept. 2, 1939, 2: 569.

Sulfanilamide, according to Schedule 4 of the English Pharmacy and Poisons Act of 1933, may be supplied to the public in England only by prescription. However, the prescribers do not always state the exact number of times that the prescription may be dispensed. Thus, there is danger that the patient may be able to obtain an excessive quantity of the drug. Therefore, prescribers should indicate on the prescription the exact number of times that it may be repeated.

The treatment of congenital syphilis with an intravenous arsenical. An analysis of 204 clinical cases. James K. Howles. South. M. J., Birmingham. Sept. 1939, 32: 940.

Of 59 patients with congenital syphilis treated at weekly intervals with mapharsen intravenously, the blood Wassermann tests reversed to negative in the following percentages of cases (by age groups): (1) 1 to 3 years, 62 percent of age group; (2) 3 to 5 years, 60 percent; (3) 5 to 10 years, 50 percent. Of 145 patients with congenital syphilis treated at weekly intervals with mapharsen and bismuth subsalicylate the Wassermann test reversed to negative in the following percentages of cases: (1) 1 to 3 years, 71.4 percent; (2) 3 to 5 years, 64.7 percent; (3) 5 to 10 years, 52 percent; (4) 10 to 15 years, 56.5 percent; (5) 15 to 20 years, 42.9 percent; (6) 20 to 25 years, 66.6 percent. The percentages of patients who had reactions to treatment were: (1) Patients treated with mapharsen alone. Immediate mild reactions, 10.55 percent; immediate severe reactions, 0.46 percent; delayed reactions, 0.16 percent; technical complications, 3.92 percent. (2) Patients

treated with mapharsen and bismuth subsalicylate. Immediate mild reactions, 10.56 percent; immediate severe reactions, 0.39 percent; delayed reactions, 0.24 percent; technical complications, 1.98 percent.

Of 46 patients (35 under and 11 over 1 year of age) treated at weekly intervals with sulfarsphenamine (intramuscularly), and with mercury injections on 6 days of each week, the blood Wassermann test reversed to negative in 24 cases. Twenty had toxic reactions to treatment.

The authors conclude that mapharsen plus bismuth subsalicylate is a satisfactory treatment for patients with congenital syphilis. The literature on the treatment of congenital syphilis with mapharsen is reviewed.

Experience with disulon, a derivative of sulfanilamide. Rafael A. Blanes. Bol. Asoc. méd. de Puerto Rico, Santurce. Aug. 1939, 31: 297.

Some months ago the author presented a preliminary report on the use of disulon in the treatment of gonorrhea [Puerto Rico Health Bull., San Juan, Apr. 1939, 3: 133]. He has used the drug further since then but even yet has not been able to arrive at absolutely definite conclusions as to its value.

The chemical name of disulon [sulfanilyl-sulfanilamide] is para-aminobenzene-sulfonyl para-aminobenzene-sulfonamide. It is a white powder with a molecular weight of 327 and it is put up in 5-grain tablets. The United States Public Health Service experimented on the toxicity of disulon and found that its therapeutic index was at least five times as favorable as that of sulfanilamide.

The author has used the drug in 30 cases of gonorrhea. It is given by mouth 30 grains a day for 6 days, followed by a rest of 5 days and then another series of 30 grains a day for 6 more days. If there is no clinical improvement during the first course the treatment is discontinued.

The author's patients were all men 17 to 32 years of age. Twenty-two of the cases were acute, treatment having been

begun during the first 3 days of the infection. Eight of the cases were chronic the duration being from 3 weeks to 3 months. All of the patients with chronic gonorrhea had prostatitis and one had epididymitis of the left testicle.

Among the 22 acute cases 18 were cured clinically and bacteriologically. Fourteen of these patients were clinically cured during the first 6 days of treatment. The urine and prostatic secretion of all the 18 cured patients were negative within 12 days of the beginning of treatment. For 2 months all these patients were examined regularly and given provocative tests but there was no sign of recurrence in any of them. In 4 of the acute cases the drug had no effect and the treatment was abandoned at the end of 6 days.

In the case of epididymitis the fever, pain, and inflammation disappeared within 24 hours after the beginning of treatment. Among the other chronic cases 3 had been given sulfanilamide without any effect and were considered sulfanilamide-resistant. Six days after treatment with disulon was begun the clinical symptoms had disappeared but the prostatic secretion was positive for gonococci. At the end of the second series of treatments both the urine and prostatic secretion were negative and have remained so up to the present.

In the 4 other chronic cases the disulon treatment had no effect and was given up after 12 days.

Among the 30 patients 3 complained of headache during the treatment, 3 of cyanosis, one of fever, and one of urticaria. The cases of severe peripheral neuritis reported by other authors were apparently caused by too high dosage.

Clinical and bacteriologic cure resulted in 73 percent of the author's cases. Disulon is more effective in acute than in chronic cases and apparently prevents complications. The total dose required for clinical and bacteriologic cure is approximately 360 grains. The best therapeutic effect is brought about by small doses—not more than 30 grains a day for not less than 4 days or more

an 6. Apparently disulon is effective in sulfanilamide-resistant cases. The toxic reactions caused by disulon are milder and less frequent than those caused by sulfanilamide.

The results obtained with this drug so far justify the hope that it will prove to be an effective treatment in gonorrheal urethritis.

A new method of treating neurosyphilis. Preliminary report. Joseph Wittenberg. *Med. Rec.*, New York. Sept. 6, 1939, 150:175.

Results of treatment are reported for patients with neurosyphilis who were given intravenous injections of an arsenical preparation immediately following the intravenous injection of ephedrine. The theory on which this method is based depends on two known facts: (1) Nearly all the arsenical injected intravenously is taken from the blood within a few minutes; (2) ephedrine, in the human being, constricts all the blood vessels of the body except those of the brain and the coronary vessels.

By the use of this method an increased amount of the arsenical injected was found in the cerebrospinal fluid. The results of treatment in these 8 patients were comparatively favorable. One patient who improved greatly (subjectively, psychologically, and serologically), and for whom the treatment was discontinued after 11 injections, later became worse. This deterioration soon ceased, however, and improvement began to gain spontaneously.

Any material rise in the blood pressure may be dangerous, and persons with an unduly high blood pressure or scleromatous blood vessels were not selected for this treatment. Each patient was examined by means of a fluoroscope, and a roentgenogram of the heart and aorta was made for record. When any doubt existed regarding the condition of the heart, an electrocardiogram was made. Experience showed that mild dilatation of the aorta is no contraindication to this treatment.

The dosage of ephedrine sulfate used was 1 grain, and mapharsen was the

arsenical selected. Results of treatment are reported in detail for each patient.

Is there any relation between the rapidity of sedimentation of the red blood cells, the leukocyte count and the response to treatment of gonorrhea treated with sulfonamides? J. Altmeier. *Arch. f. Dermat. u. Syph.*, Berlin. Aug. 22, 1939, 179: 279.

It is a generally accepted opinion that the drugs of the sulfonamide group injure gonococci or other infecting bacteria so that they can be destroyed by the defensive forces of the body. When the body is first infected it does not have any defensive forces available and some time is required for the development of effective antibodies. During the time required for the development of such antibodies sulfonamide treatment is not apt to be effective.

Little is known about processes of immunity in the body in gonorrhea. Apparently the substances demonstrated by the gonoreaction are not true antibodies and their appearance, therefore, does not indicate the time for beginning sulfonamide treatment.

Gensler claims that the change in the body necessary before chemotherapy of gonorrhea can be effective is shown by a change in the rapidity of sedimentation of the red blood cells and in the leukocyte count. In all of his cases in which uliron treatment was successful, there was an increase in the number of leukocytes and in the rapidity of sedimentation of the red cells before the treatment. Both of these values fell to normal during the treatment. But in patients in whom the treatment was not successful there was no increase in leukocyte count or rapidity of sedimentation before treatment was begun. In these cases he tried to bring about increased rapidity of sedimentation and leukocytosis by preliminary vaccine treatment.

The author tested the truth of this theory on 115 patients with gonorrhea at the University Dermatological Clinic of Frankfurt am Main. The patients were each given two series of treatment with

disseptal C. During each series 2 tablets were given 4 times a day for 5 days. There was an interval of 6 days between the two series. Leukocyte counts and sedimentation tests were made before and after treatment. The tables showing the details of the results do not confirm Gensler's theory. Patients who did not have the changes in white count and sedimentation rate described by him were cured and ones who did have such changes were not all cured.

A case of symptomatic zoster is described in a woman who was treated for gonorrhea of the cervix with disseptal C.

Clinical observations on the mode of action of uliron and disseptal B and C in the body of the gonorrhea patient.

Karl Bruder. Arch. f. Dermat. u. syph., Berlin. June 29, 1939, 179: 183.

The action of the sulfonamide compounds uliron and disseptal B and C was tested in 51 patients with gonorrhea.

Disseptal B and C were absorbed from the gastro-intestinal tract more rapidly and more completely than uliron. In one case in which the conditions of absorption were better than the average it was found that 15 percent of the dose of uliron was excreted unabsorbed in the stools while only 7 percent of the disseptal B was unabsorbed in a similar case.

In the blood the drugs could be demonstrated both in the serum and the erythrocytes. The content of disseptal B was higher than that of uliron. For uliron and disseptal B the drug content of the serum was much higher than that of the erythrocytes, while for disseptal C the opposite was true. None of the 3 compounds could be demonstrated in the blood later than the 6th day after their administration was stopped. Therefore, an interval of 8 days between 2 series of treatments is sufficient.

The amount of uliron that appeared in the urine either free or combined was 35.5 percent; of disseptal B, 58.1 percent; and of disseptal C, 65.6 percent. The amount of combined substance varied from 0 to 50 percent. Excretion in the urine was complete by the end of 7 days after the medication was stopped.

Disseptal B was demonstrated qualitatively in the spinal fluid and in breast milk, though the amounts could not be measured.

Hecht's method of demonstrating the drugs in the body fluids was used for this pharmacologic part of the study.

In the clinical part of the study there was evidence that the action of the drug consists in injuring the bacteria so that their destruction can be completed by the defensive forces of the body. The failure of sulfonamide treatment was never found to be due to too small doses or too low a concentration of the drugs in the blood. It is obvious that chemotherapy alone without the use of local measures can have no effect on foci of gonococci hidden in crypts and gland tubes and inaccessible to the blood current. An examination of the cases in which the treatment failed showed that the patients were in poor general condition or were suffering from other diseases also.

No difference could be demonstrated in the effectiveness of uliron and disseptal B. The use of disseptal B is recommended because of its more complete absorption and its more rapid and complete excretion. Serum concentrations of about 5 mg. percent uliron and disseptal B and about 1 mg. percent disseptal C are sufficient for cure provided the defensive forces of the body are in normal condition.

Disseptal exanthems are toxic in the majority of cases. They are due to an accumulation of the drug in the tissues and possibly in some cases to an association of the drugs with other endogenous or exogenous toxins and to great individual differences in sensitiveness to the disseptal compound.

There are some cases of true allergic disseptal exanthem but they are much rarer than the toxic cases. A case of this type is described and on the basis of the blood changes seen in several cases the possibility of sensitization by the usual intermittent treatment is discussed. The results of subcutaneous and intracutaneous skin tests suggest that it is possibly not the drugs themselves that

use the allergy but unknown disepthal derivatives that develop in the body.

he drugs in the treatment of congenital syphilis. John E. Ashby and Halcuit Moore. Texas State J. Med., Fort Worth. Sept. 1939, 35: 353.

The results of treatment of 250 patients with congenital syphilis are presented with an analysis of those cured and of those whose blood tests remained positive after treatment was completed. All possible methods of diagnosis should be employed to determine the actual presence of a syphilitic infection in such cases, and no treatment should be administered until it has definitely been established that a syphilitic infection is present. The percentages of cases in which blood tests became negative as a result of the use of various drugs were as follows: (1) From the use of neoarsphenamine, 65 percent; (2) mapharsen, 48 percent; (3) soluble bismuth (thiobismol), 65 percent; (4) bismuth in oil (insoluble bismuth), 70 percent; (5) sulfarsphenamine, 85 percent; (6) stovarsol, 83 percent. Apparently stovarsol combined with soluble bismuth, and mapharsen combined with soluble bismuth, produced a higher percentage of good results than the other drugs. Stovarsol is definitely advantageous due to its ease of administration and the fact that very young infants can tolerate it. In mapharsen treatment a considerably higher dosage of the active principle of arsenic may be administered without reactions.

Reactions followed the administration of the various drugs as follows: Neoarsphenamine, 0.505 percent of 2,379 doses were followed by reactions; mapharsen, 0.251 percent of 1,178 doses; thiobismol, 0.251 percent of 3,066 doses; bismuth in oil, 0.446 percent of 448 doses; stovarsol, 4 reactions (0.322 percent) in 1,240 weeks of treatment.

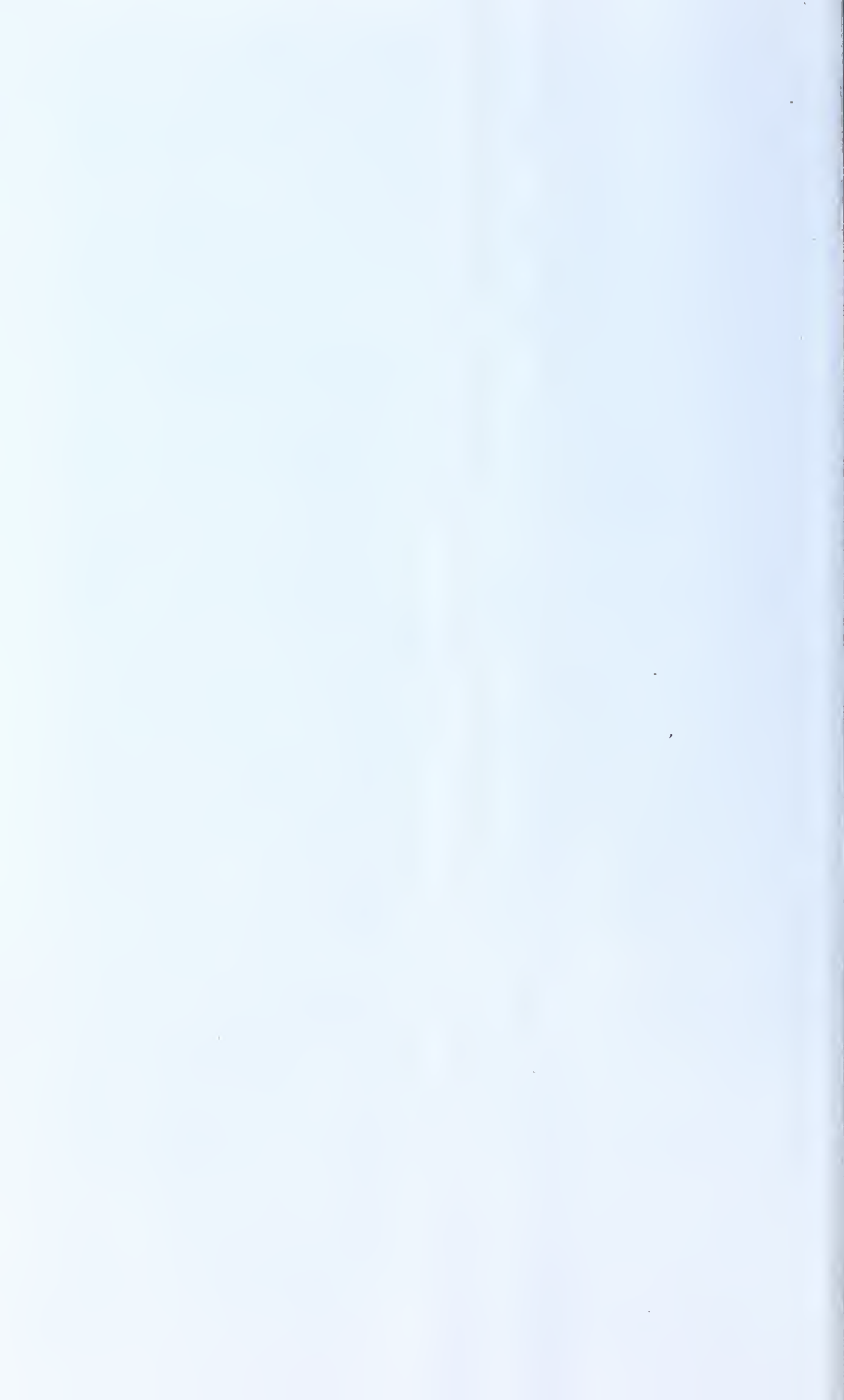
Ophthalmia neonatorum. Leslie C. Drews. J. Missouri M. A., St. Louis. Sept. 1939, 36: 366.

The etiology, diagnosis, clinical course, prophylaxis, treatment, prognosis, and complications of ophthalmia neonatorum are discussed.

Prophylaxis should include antenatal treatment of infected mothers with possibly the use of antiseptic vaginal washes at the onset of labor. As soon as the baby is born the external portion of its eyelids should be gently cleansed with 1:10,000 mercury bichloride or with plain water. A drop of 2 percent silver nitrate, freshly prepared or used from sealed wax ampules, should be instilled into the conjunctival sacs and after 5 or 10 seconds the sacs should be washed thoroughly with normal saline solution.

Treatment is designed to remove bacteria by mechanical washing, increase the patient's resistance, avoid or relieve excessive swelling of the lids or conjunctiva, and destroy the bacteria. Irrigation with a nonirritating solution, such as 2 percent sodium biborate, should be repeated often. Mild antiseptics such as neosilvol (20 percent) and metaphen (1:2,500) should be used alternately every 2 to 4 hours. Silver nitrate ($\frac{1}{2}$ to 2 percent), which was formerly used freely, is now reserved for cases in which the period of virulent secretion is protracted, and the cornea must be protected from the drug. The use of nonspecific protein therapy (such as boiled milk given intragluteally) is reliable and effective. Striking results with sulfanilamide and neoprontosil by mouth have been reported. Free canthotomy should be performed to relieve the pressure of the swollen lids upon the cornea. Scarification of the bulbar conjunctiva has been advised to relieve severe chemosis. Other operative procedures are sometimes advisable.





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UNITED STATES PUBLIC HEALTH SERVICE
Thomas Parran, *Surgeon General*

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Syphilis Control

Principles of Case-finding and Case-holding

HELEN E. WOODS

AT THIS stage in the history of syphilis control it is an acceptable premise that case-finding and case-holding are important adjuncts to any control program. A reiteration of the values of such emphasis would be trite and shopworn. The goals which we set out to achieve are rather well understood today. In contrast to our achieved clarity of purpose there remains a vast lack of comprehension of the problems which beset us and foil our efforts. There is need for examination of methods and for a penetrating evaluation of results. The process by which we attain success or meet failure is still almost an unexplored field.

The failure to conquer syphilis by mere routines and regulations has already been clearly demonstrated. Too often the practical task has been left to those least able to perform it. Their perfunctory efforts have not been motivated by interest in the job and have not been based on a foundation of preparation for it. Syphilis, as a community problem, has gained recognition in public consciousness leading to action. In fact, we have veered from the indifference of some years ago to very energetic activity.

In examining briefly the public attitude which has shaped changing policies and emphases, it seems apparent that this attitude changes much more slowly than the forms of practice it advocates.

NOTE.—Read at Regional Institutes on Syphilis Epidemiology, auspices of the Division of Venereal Disease Control, New Jersey State Department of Health, April 1939. The author is chief social worker of the Institute for Control of Syphilis, Hospital of the University of Pennsylvania.

Both in its former indifference and in its present drive for action is reflected a great deal of contempt toward those who have syphilis. It would sometimes seem as though the patient, rather than the disease, is seen as the menace to society, and hence some of our practices both in clinics and health agencies are ruthless.

In spite of this remnant of a punishing attitude toward the patient with syphilis, tremendous progress has been made in his behalf for the public health against further inroads by this disease. Increased provision for treatment made available for those who need it is an important factor in bringing and holding more patients to treatment. Fewer patients forego medical care now because of lack of funds or inaccessibility of clinics. The outlay by communities for these facilities is certain to pay dividends in improved health of patients and protected health of others. It is quite reasonable that the community which makes good treatment possible for those who suffer from syphilis should require that patients shall take treatment as long as they are able to transmit the infection to others. In the interest of the common good, therefore, the patient loses some measure of his freedom of choice as in other beneficial provisions such as compulsory education and vaccination.

The methods employed to insure the regular and complete treatment of patients must vary somewhat to meet the needs of different localities and of varying patient groups. In general, however, there are principles applicable to all. A fair, considerate procedure with patients and appreciation of their problems are basic

to any sound program. This is not to say that there need be no enforcement measures, for these are essential. It is to say that such measures should be used judiciously and applied with care to protect patients from abuse and truly serve the interest of public health. History gives us ample evidence that emphasis on compulsion alone (exploiting a fear motive) has not decreased the prevalence of syphilis. It has merely driven the disease into hiding. Syphilis is all too easily concealed even in this day of widespread uncovering mechanisms.

It is not too difficult in a community of stable population to keep a vigilant control of those patients in whom syphilis has been discovered. It is difficult to bring under medical supervision the undiscovered cases. Where it is known that drastic measures are too readily employed to keep patients under control, there is a remarkably low proportion of new patients who seek treatment voluntarily. The element of fear is more likely to hamper than to help a control program. It does not prevent exposure nor keep the patient under treatment. More often it prevents his seeking good medical advice. We need only to consult the archives of sociology and psychology to find examples of the failure of fear as a deterrent force. Fear of consequences has never lessened the incidence of crime, illegitimacy, or other social ills. Therefore, we must look to some other and more positive influence to bring existing patients with syphilis under treatment and to prevent further dissemination of the disease.

Everywhere now we hear the proffered advice to treat syphilis as any other communicable disease. This is a sound suggestion if by it is meant an unemotional attitude on the part of public and health authorities which will assure considerate, sympathetic, and fair treatment of patients. A change would be required in much of our present court procedure which attempts to control syphilis by considering it as a moral issue rather than as a communicable disease. If the patient, too, can think of syphilis as any

other disease he will seek and accept treatment with less difficulty.

Let us look at syphilis from the viewpoint of the patient and see what we must do to help him. A case of typhoid fever, scarlet fever, or other communicable disease in any home brings with its necessary isolation the sympathy and assistance of neighbors. Symptoms are acute and the suffering patient is attended by his devoted family. If syphilis is the disease, can the patient expect the same neighborly sympathy? The answer is obvious. What of his family? Will they attend with the same devotion? One factor is that the patient with infectious syphilis is not acutely ill. But this is not the only difference which distinguishes it from other diseases. The fact remains that the infection is usually acquired through intimate personal contacts. Despite the changes which have occurred since the Victorian era, there is inhibition concerning free discussion of matters related to sex. In our monogamous society with American standards, promiscuity and extramarital relations are taboo with a consequent threat to family harmony when syphilis enters the picture. The patient and his family have a great deal to face by the very implication of syphilis. Readjustment is practically always possible, but the process is not simple.

In addition to meeting the problems of syphilis in his family, the patient is often faced with the practical danger of losing his employment. This danger is increased today with the growing publicity given to control of the disease. Many employers are becoming "syphilis conscious" and, without full knowledge of the facts, fear to retain in their service anyone who is infected, regardless of the kind of job or stage of disease which the patient has. Work is a practical necessity and if this is threatened by discovery of his disease or by his attendance at a clinic, the patient cannot be expected to fall in line submissively with our well-laid plans. He therefore has sufficient cause to resist the control we have over him after he presents himself for exam-

nation and treatment and to resent the loss of freedom it brings.

Perhaps it is timely to raise the question, Can the patient who has syphilis ever be expected to adjust to the situation so that he voluntarily takes responsibility for himself? Can he have sufficient concern for others to endure a long course of unpleasant treatment at expense or inconvenience to himself with added risk of losing work, social status, or even the security of home ties? Many of our policies and procedures would suggest that we do not believe the patient will conform and that effort must be directed toward overcoming his resistance. Could it be that we have expected too little and have, therefore, been repaid by little in way of patient responsibility?

The normal person is interested primarily in himself. He has also a community interest, for he cares deeply about the approval of his fellow men. He feels himself to be part of a large social group and participates in concern for that group. Protective public health measures are entirely comprehensible and acceptable to him. When the patient with syphilis recognizes that he shares in the general health protection of a public program, he can appreciate the fairness of regulations when they require something of him. Even compulsory measures when necessary and applied with justice can be understood by the patient.

It is most important, then, to give the patient an opportunity to take this responsibility. The need for it may have to be pointed out to him, and he may require assistance in hurdling some of the practical obstacles. Giving the patient as much responsibility as he can take, or rather sharing it with him, can do much to preserve his self-esteem and initiative. These are vital forces. If through thoughtless handling they are destroyed neither the patient nor the community is well served, and a new kind of dependency may spring from the experience. While some few will always need to be directed and to have decisions made for them, most people do best when given the opportunity for self-direction. A

clinic or health department with a policy which takes these factors into consideration can go far in case-holding with minimum expense, and it also finds that patients with new infections voluntarily seek its service.

The first and most essential step in the control of syphilis is taken at the point when each patient begins his treatment. The establishment of rapport with the patient and a clear agreement between him and his physician or clinic as to plans of procedure may accomplish all that is needed in case-holding, control of infectiousness, case-finding, and general education within his own circle of friends. This is achieved most effectively when the patient feels it to be a joint plan in which he is carrying a good share of the responsibility. In reality, we are dependent upon the full participation of the patient if our goal is to be realized. In general, the division of responsibility is as follows: (1) The community provides treatment facilities; the patient presents himself for treatment and accepts it in spite of the obstacles. (2) The community provides adequate instruction and assistance to the patient in adapting himself to a difficult situation; in response to this the patient observes precautions and protects others from infection. (3) The community provides the service to assist in arranging for examination of contacts; the patient's part is to divulge the identity of his contacts and sometimes to approach them regarding examination.

The partnership with the patient which is implied here can be brought about only by a clear, direct, and comprehensive discussion with the patient. It necessitates a sensitive appreciation of the position in which the patient finds himself and a clear evaluation of the amount and kind of guidance he needs. Of basic importance is the inclusion of informative material during this interview with the patient. Despite present efforts at education, much confusion regarding syphilis still prevails, and the failure of many patients to follow advice is based on misunder-

standing of important points. Instruction should, therefore, include some description of the disease, its course, and the effect which treatment has on it. Public health aspects of syphilis and the requirements of the local health department should be pointed out. Some discussion of the transmission of syphilis should lead naturally into the subject of the patient's intimate contacts, who should be examined, and his service to them by making their examination possible. The practice of telling the patient things which are not scientifically correct just for the purpose of "impressing him with the need for treatment" is outmoded and unsound.

For the patient who fails to report with regularity for treatment, some form of attendance follow-up is necessary. It is wasteful of both the patient's efforts and treatment facilities to administer a few doses of drugs and then have the course interrupted. Added to this is the serious danger to public health from partially treated infectious cases because of their tendency to relapse into infectiousness.

The methods of restoring the lapsed patients to treatment must be determined by the reasons for the lapse in attendance. These reasons vary with individuals and in general vary with different communities, e. g., inaccessibility of treatment centers may characterize the problems of one district while a transient population may baffle the health agencies in another. It is important, therefore, that any community direct its efforts toward studying its needs, and shape its policies of service accordingly. Even the manner of communicating with individual patients may call for special consideration if the effort is to be productive of results. Knowledge of the community and an understanding of the patient's circumstances gained at his initial visit should serve as guides for follow-up procedure.

Practical policies related to the transferring of cases in the shifting population of today are most important. Reciprocal agreements with other State and local treatment centers are at pres-

ent quite workable because of official support given to syphilis control. Our failure to effect the smooth transfer of cases too often lies simply in neglecting to inform the patient that transfer is possible. Many times patients leave town without notifying the clinic and without the knowledge that treatment facilities near their new place of residence stand ready to accommodate them.

Two essential methods are used in case-finding as applied to syphilis. The first, serologic surveys, has come into wide use and serves to uncover many cases of latent infection which might otherwise escape the notice of the patient himself. The second method is that of epidemiologic investigation, a tracing of each chain of infection through examination of those in personal contact with the known syphilitic patient. By the second method, it is usually possible to find the infection while it is early, sometimes before serologic tests can detect its presence. This timely discovery of the disease increases the patient's opportunity for cure by early treatment and reduces the danger to public health by a shortened period of infectiousness.

It is essential that family contacts be examined if they have been exposed to the infection. The examination of children is indicated when a known infection in the mother antedates their birth or if one child is found to have prenatal syphilis. In rare instances a child may acquire the disease accidentally from an infected adult—this depending largely on the site of the adult's lesions, the intimacy of living arrangements, and general hygiene. A marital partner should always be examined if possible.

The arranging of contact examinations outside the family is, perhaps, the most difficult task in any syphilis control program and a most important one. In this we are entirely dependent upon the patient himself, and the rapport formerly described is of primary significance. It is asking a great deal of patients to request disclosure of details in their private lives including the identity of

their sexual intimates. Unless the patient's confidence has been gained, he is unlikely to divulge the needed information, and there is no way to force him to do so. Any patient who fears the consequences of a disclosure can easily seek refuge in plausible explanations of inability to trace his contacts. Therefore, in order to achieve any success in this method of case-finding, it is necessary to recognize the patient not only as a partner but as the leader.

Many times I hear the opinion expressed that the patient cannot be expected willingly to participate in such a procedure, and only through forceful urging will he respond at all to the request. If this is so, examination of the method of presenting the matter is in order. The patient who fully understands the value of an examination for his contacts will gladly make it possible when he is confident that clumsy handling will not lead to difficulty for himself and those involved. It is a sounder and more positive appeal to help him see it as a service to his friends who, if unwarned, might suffer the consequences of a serious disease. A negative approach only drives him to seek a way to project blame elsewhere, in which case he is certain to name only his enemies and never those whom he would protect.

There are decided advantages in having a patient make direct arrangements with his contacts for their examination, and many patients with a sense of responsibility choose to do this. When this does not seem possible, the patient may entrust the task to a public health representative.

In order to be effective, the approach to the contact of a patient with syphilis must be individual, personal, and confidential. The person thus approached by a stranger who has knowledge of his intimate affairs is likely to be on the defensive until assured by the manner as well as the words of the interviewer that the procedure is motivated by a genuine interest in him. Instead of meeting a contact with an accusation which he probably fears, he is met with a concern that he

might have been a victim of so serious a disease as syphilis. An authoritative approach in requesting the examination seems like a short-sighted method when it is realized how much of later accomplishment depends upon enlisting the full cooperation of the contact. Added to this practical point, it is rather harsh treatment of a person who may be suffering from a serious disease. At the time of reaching a contact to suggest examination there is only hearsay evidence that he has even been exposed to syphilis, and it still may develop that he is uninfected in spite of exposure.

The whole question of finding cases of syphilis and holding them to adequate treatment is related directly to the manner of dealing with those who have the disease. It is an infection acquired usually in the late adolescent and early adult years—a vigorous, independent, and self-directing group. Reliable statistics show that approximately 70 percent of persons with syphilis under treatment came to medical attention when the disease was already in a late stage. It is probable that the majority of infections at present are discovered by routine serologic tests. If we are to accomplish a decrease in the incidence of syphilis we must do more—we must treat infections in their beginning stages, thereby shortening the period of hazard to public health. This means that patients themselves must request examination upon the appearance of symptoms. Until patients in greater numbers voluntarily present themselves for medical advice as soon as infection is suspected, we have made little progress. To begin treatment when the disease is late is to help those cases in hand, but it does not prevent the further spread of syphilis, for the disease has doubtless already been transmitted to others.

Again may I suggest that the patient is the key person in the syphilis control program. The normal person does not want syphilis and does not want to spread syphilis. He is grateful for the opportunity to rid himself of a dreaded disease, to protect others from acquiring it, and to advise those of his associates who may have it. He cannot

do this, however, if our attitude and methods are so forbidding that he keeps clear of proper medical resources when he needs them most. He cannot be expected to shoulder responsibility if he is ill-informed. He needs to feel accepted in the community and certainly in the clinic, regardless of his diagnosis. He needs to have reduced risk of unnecessary job-loss and of ostracism by his fellow men. All of this requires more and better education of the gen-

eral public as well as the patient.

It may be that the above suggestions sound too general, too theoretical. They can have practical value only when applied in each individual case, in each operating clinic or office, upon every occasion for discussion of the subject with employers or other lay members of a community. In short, the day-to-day task of everyone engaged in the syphilis control program offers the most solid basis for progress.

Progress in Venereal Disease Control During Fiscal Year 1939

VENEREAL DISEASE control activities in the United States increased markedly during the period from July 1, 1938 to June 30, 1939. The LaFollette-Bulwinkle Bill (Venereal Disease Control Act of May 24, 1938) provided the basic funds as well as the additional stimulus for a venereal disease control campaign in which the U. S. Public Health Service cooperated with State and local health authorities. Under the provisions of the Act, the sum of \$3,000,000 was made available for the first year of the program. Of this amount, the sum of \$2,400,000 was allotted by the U. S. Public Health Service to the health departments of the States and Territories. Under the matching requirements laid down by the Surgeon General, State and local funds to the amount of approximately \$4,300,000 were used to supplement the Federal allotment for venereal disease control.

The progress achieved through the expenditure of these funds is plainly demonstrable in the rapid extension of treatment facilities, of laboratory services, of research and training programs, as well as in the rise of popular response

to and interest in the venereal disease control program.

During the fiscal year 1939, the number of clinics for the treatment of venereal diseases increased over 30 percent. By June 30, 1939, the number of clinics as reported to the U. S. Public Health Service stood at 2,405; while the number reported on July 1, 1938 was 1,746. With the exception of three, every State and Territory in the Union maintains or gives aid to clinics in which venereal disease patients may obtain free or part-pay treatment. In one of these areas, laboratory services and an educational program are administered by the State while the actual treatment services are provided by the county governments. In another, while no clinic facilities are available, the health department provides free drugs to private physicians for the treatment of all patients. In the third, initial steps have been taken to establish satisfactory therapeutic services for the control of the venereal diseases.

An encouraging indication of progress, which emphasizes the increasing spirit of cooperation between organized treatment centers and State health authorities, may

e observed from the fact that over 90 percent of the venereal disease clinics were providing monthly activity reports to State health officers by the close of the fiscal year 1939, whereas during the preceding year only 60 percent of the clinics in existence at that time cooperated in such a manner.

In order to determine the nature and extent of the venereal disease problem, as well as to measure the progress of venereal disease control activities, adequate statistical reporting is necessary. The most striking indication of progress in this respect is the fact that during the fiscal year 1939, the U. S. Public Health Service aided State departments of health in installing central tabulating systems for the reporting of venereal disease activities in areas including 500 clinics serving a population of 38,000,000. As the result of this program, a mass of data concern-

ing venereal disease morbidity is being acquired rapidly.

The number of persons with venereal disease brought under treatment for the first time in organized clinics throughout the United States increased from 197,000 in 1938 to 315,000 in 1939. The number of treatments administered in clinics increased from 5,200,000 in 1938 to 8,000,000 in 1939; and the number of patients discharged from clinics as arrested or cured rose from 78,000 in 1938 to 103,000 in 1939. During the fiscal year 1939, approximately 2,300,000 laboratory tests for diagnostic and control purposes were performed by or for clinics; and 3,200,000 doses of arsenical drugs were administered to clinic patients. These data are merely partial indexes that treatment and laboratory facilities and services increased between 30 and 85 percent during the fiscal year 1939 (table 1).

TABLE 1.—*Comparison of venereal disease clinic activities in the United States—fiscal years 1938 and 1939*

	Fiscal year 1938	Fiscal year 1939	Percent increase during 1939
1. Number of venereal disease clinics reported as functioning during fiscal year.....	1, 746	2, 405	37. 7
2. Number of venereal disease clinics reporting activities to State and Territorial health departments.....	1, 122	2, 085	85. 8
3. Number of venereal disease patients brought under treatment for first time in clinics ¹	197, 303	314, 594	59. 4
4. Number of treatments administered in venereal disease clinics ¹	5, 177, 827	7, 923, 958	53. 0
5. Number of doses of arsenical drugs administered in venereal disease clinics ¹	1, 854, 735	3, 166, 342	70. 7
6. Number of patients discharged from venereal disease clinics as arrested or cured ¹	78, 042	102, 880	31. 8
7. Number of laboratory tests performed by or for venereal disease clinics ¹	1, 323, 177	2, 350, 695	77. 7

¹ Activities reported to State health departments by cooperating clinics.

Study of the activities of the State and Territorial health departments indicates that the number of tests for syphilis and gonorrhea performed in State-owned or controlled laboratories rose from 4,000,000 in 1938 to 6,000,000 in 1939. Free arsenical drugs distributed to private physicians and clinics increased from 2,800,000 doses in 1938 to 4,700,000 doses in 1939. With the recognition of the newer chemotherapy in the treatment of gonorrhea, State and Territorial health departments reported

the free distribution of 3½ million 5-grain sulfanilamide tablets during the fiscal year 1939. Free drugs for the treatment of persons with venereal diseases are provided in every State and Territory. In 26 States and Territories, free drugs are provided to all persons regardless of economic status (compare with 14 States providing such service in 1938); while in the remaining States and Territories, such drugs are provided only to indigent, semi-indigent, or other special cases (table 2).

TABLE 2.—*Comparison of activities of State and Territorial health departments—fiscal years 1938 and 1939*

	Fiscal year 1938	Fiscal year 1939	Percent in- crease dur- ing 1939
1. Number of States and Territories employing venereal disease control officers.....	34	52	52.9
(a) full-time.....	29	32	-----
(b) part-time.....	5	20	-----
2. Number of State and Territorial health departments with separate divisions or sections of venereal disease control.....	27	53	96.3
3. Number of States and Territories distributing free drugs.....	47	53	12.8
(a) regardless of economic status.....	14	26	-----
(b) to indigents or special cases only.....	33	27	-----
4. Number of doses of arsenical drugs distributed free by State or Territorial health departments.....	2,799,110	4,677,757	67.1
5. Number of tests performed by State laboratories.....	4,462,684	6,209,705	39.1

By the close of the fiscal year 1939 each State in the Union (including the Territories and the District of Columbia) had established a separate bureau, or subdivision of an already existing bureau, for the control of venereal diseases; while during 1938, such divisions or sections existed in but 27 of the 53 areas. In 1938, full-time venereal disease control officers were employed in 29 States, and part-time officers were employed in 5 States; but in 1939, 31 States (and Puerto Rico) employed full-time control officers, and 17 States, Alaska, Hawaii and the District of Columbia, employed part-time officers. Every State in the Union now employs at its own expense, or through county health departments, case-finding and case-holding workers.

Progress in prenatal and premarital detection of syphilis has been achieved. Nineteen States now require examinations including serologic tests for syphilis of all applicants for marriage licenses, and 15 States require physicians to perform blood tests for syphilis on expectant mothers.

Educational activities among laymen and physicians have expanded. The radio and press have responded generously in their support of the venereal disease control program. Popular response has caused industry, labor, church, and school to formulate programs dealing with the

social aspects of venereal disease control. Postgraduate training centers in venereal disease control for physicians and nurses have been expanded with the support of the United States Public Health Service. During the fiscal year 1939, financial assistance was provided to postgraduate training centers located in nine of the leading universities.

Research activities dealing with the various aspects of venereal diseases were continued during 1939. Numerous investigations, undertaken by the United States Public Health Service in cooperation with outstanding medical groups, were begun or continued during the period. Of special merit are a series of research-demonstration projects organized during the fiscal year in cooperation with State and local health departments. These projects, covering rural as well as urban areas, have been designed to demonstrate various methods of venereal disease control and treatment under a wide variety of conditions.

Although great progress has been achieved in the field of venereal disease control, much additional work over a long period of time is essential. In recognition of this, the Congress, in accordance with the authorization contained in the Venereal Disease Control Act of 1938, appropriated the sum of \$5,000,000 for the prosecution of the program during the fiscal year 1940.

PUBLIC HEALTH ADMINISTRATION

Control of syphilis in a Southern rural area. A preliminary report. L. E. Burney. *Am. J. Pub. Health*, New York. Sept. 1939, 29: 1006.

The U. S. Public Health Service in cooperation with the Georgia State Department of Public Health and the Glynn County (Georgia) Board of Health has established a mobile clinic for the treatment of syphilis in the Negroes of 3 coastal counties of Georgia—McIntosh, Glynn, and Camden. The area in which the mobile clinic operates consists chiefly of pine woods and swamps, and it is sparsely settled. The chief industries in which the Negro patients are employed are turpentine, lumber, and fishing. The Negroes live away from the highways, back in the woods, and transportation to central stationary clinics would be very difficult for them. Twenty-seven percent of these Negroes were found to have positive tests for syphilis. During the 11-month period previous to the preparation of this report, 2,258 patients were examined and treated. The author describes the equipment and personnel required for the clinic and the unusual methods used to keep patients under treatment. He presents graphs and tables showing the number of positive blood tests in the Negroes (by age groups) of the three counties, and tables showing classification of the patients by age and stage of infection.

He concludes that (1) the mobile clinic has many advantages over the stationary clinic in the control of Southern rural Negroes because it can cover a large territory in a short time, it can be easily and quickly operated, it is interesting for the patients, it is a good advertisement for general health programs, and it is very economical; (2) house-to-house canvass for obtain-

ing blood tests is the most efficient method of finding cases; (3) case-holding is essential to the success of the program; (4) the Negro in rural Southern areas can be slowly taught the facts about syphilis and the necessity for treatment. This can best be accomplished by talking movies (although there is none at present for such an audience), simple literature, and through Negro ministers and school teachers.

Some problems in the control of syphilis as a disease. John H. Stokes. *Am. J. Syph., Gonor. & Ven. Dis.*, St. Louis. Sept. 1939, 23: 549.

In this detailed analysis of important problems in the control of syphilis, the author discusses (1) alcohol, prostitution, personal venereal disease prophylaxis, (2) contact-tracing and epidemiology, (3) education compared with legal control measures, (4) problems in diagnosis, (5) some problems of treatment, (6) the education of the clinician and the cooperating doctor, and (7) some administrative practicalities.

In discussing laws for the control of syphilis, Stokes states that he sides with education rather than force. Premarital and prenatal antisiphilic laws can be made useful for educational purposes if carefully drawn and intelligently interpreted by physicians, health officers, and the courts; and if they are not defeated or discredited by premature enactment and inadequate serologic and other setups.

Any State or national organization for the control of syphilis must provide (1) the basic equipment for performance of the tests, (2) a service for the collection, handling, and reporting of specimens, (3) a mechanism for expert interpretation of doubtful or complex findings. No State has yet made more than a fair beginning in the provision of referee or consultant service. A serologic test is a fallible product of its performer and of performance conditions and varies with them from worthlessness to near-perfection. Modern syphilologic labora-

tory service should provide for prompt and trustworthy dark-field, blood serologic, and cerebrospinal fluid examinations. Instructions are given for the collection of dark-field, blood, and cerebrospinal fluid specimens, and the proper interpretation of laboratory findings is discussed.

Sixteen symptoms and 20 signs of syphilis are tabulated, and the importance of physical clues in the diagnosis of the disease is emphasized. Thirteen known facts about the infectiousness of syphilis are tabulated with 20 doubtful or unknown factors. The author says that although there is little known about actual infectiousness, "treatment to noninfectiousness" is commonly discussed as if it were a definable entity which may be achieved by providing enough free drugs and enforcing laws.

Treatment problems are discussed briefly and special warnings are given regarding treatment of the chronic relapser and the syphilitic pregnant woman. The "best" treatment of early syphilis is outlined, and Stokes particularly emphasizes the importance of adhering strictly to an effective schedule of treatment. Public health officers should be more deeply concerned with the patient who "becomes seronegative" easily than with the patient who, in spite of massive treatment by a variety of methods, remains "seropositive."

In discussing the education of the clinician and the cooperating doctor, Stokes suggests that 2 years be accepted as the minimum time for the training of a consultant, one year for a venereal disease control officer or chief of a city or regional clinic, and 1 to 6 weeks for the front-line clinic medical staff and the general practitioners who extend cooperation in the average small community.

The clinic should be readily accessible to its prospective patrons, it must be open at night to treat those who work during the day, and it must be so arranged that privacies and decencies of the patients will be preserved. The staff must be friendly, tolerant, seriously interested in the patient, and devoted to the work.

Prenatal care. (An eleven year study of the Dalhousie University Public Health Center Prenatal Clinic.) A. L. McLean and W. G. Colwell. *Canad. M. A. J.*, Montreal. Oct. 1939, 41: 382.

During the years 1925-1935, inclusive, 790 women attended the prenatal clinic, Halifax, for care and advice, and the recorded data on their 1,132 pregnancies are analyzed. Although special endeavor had been made to contact patients as early in pregnancy as possible, only 16 percent of all the patients presented themselves for examination before the fifth month of pregnancy.

The results of serologic tests for syphilis were recorded for 669 of the 790 women, and 14 percent had a positive Kahn reaction. In order to compare the effect of syphilis on pregnancy in positive and negative reactors, the results of 2,429 pregnancies were tabulated. This table shows that among the 333 with positive serologic tests and the 2,096 with negative serologic tests, the percentage of living births is definitely higher (88 percent) in the negative group than in the positive group (78 percent), and the rate of stillbirths is definitely lower in the negative group (3 percent), the rate in the positive group being 9 percent. In the positive group premature, living infants comprised 6 percent of the births and abortions 7 percent, and among the negative group they were 3.5 percent and 5.5 percent respectively. The percentage of fetal deaths was significantly higher among women with positive tests (15.9 percent), or nearly double that of the negative reactors (8.5 percent).

Annual report for the year 1938 of the Division of Venereal Disease Control, British Columbia Board of Health. Bull. British Columbia Board of Health, Victoria. Sept. 1, 1939, 9: appendix 2, 113 pages (mimeographed).

This report summarizes the activities of the division of venereal disease control during the calendar year 1938. It presents a statistical analysis of cases of venereal diseases reported during the

year in British Columbia, and it gives a detailed description of the various clinics established for the treatment of such diseases. Thirty-one tables are presented which tabulate the cases reported by disease, age, sex, nationality, place of birth, employment status and occupation, sources of infection, whether treated by clinics, reason for termination of treatment, marital status, types of treatment given, and laboratory reports. Five charts are included which show the organization of the division of venereal disease control, the organization of the Vancouver venereal disease clinic, and the floor plans of the Vancouver, New Westminster, and Nanaimo clinics. Four statistical maps of British Columbia are given which show by statistical areas the total number and the rate per 1,000 population of all cases of venereal diseases and of the number reported for the first time during 1938. Nineteen graphs are presented illustrating the number of cases reported from 1929 to 1938; and the number reported for the first time in 1938 by source of reference, age groups, sex, marital status, nationality, occupation, and treatment.

The total number of cases of venereal diseases reported during 1938 was 3,034 (1,430 cases of syphilis and 1,604 of gonorrhea). Of the cases of syphilis (937 men and 493 women), clinics reported 717 and private physicians 597. Of the cases of gonorrhea (1,252 men and 352 women), clinics reported 1,059 and private physicians 523. Other institutions reporting small numbers of cases included hospitals, mental institutions, tuberculosis institutions, and the provincial penitentiary.

New courses in syphilis and its control.

Health News, Albany. Sept. 25, 1939, 16: 158.

Postgraduate courses in syphilis and its control are offered by the New York University College of Medicine during 1939-40. The courses are made possible by grants from the U. S. Public Health Service and the New York State Depart-

ment of Health. They are designed to occupy the full time of students. Three types of courses are offered—a refresher course of 8 weeks, a refresher course of 4 weeks, and work in syphilology for a full academic year including both clinical and public health aspects. The various departments of the College of Medicine and the bureau and field services of the New York City Department of Health are available for experience and observation. The wards and clinics of Bellevue Hospital and the clinic of the College of Medicine provide unusually ample material. For information concerning these courses, physicians should communicate with the Division of Syphilis Control, State Department of Health, Albany, N. Y., through which a limited number of fellowships are available.

Ratings of the bureau of laboratories in the 1938 evaluation study. Earle K. Borman. J. Connecticut M. Soc., Hartford. Sept. 1939, 3: 506.

This is a report of the work of the bureau of laboratories of the Connecticut Department of Health in its participation in the studies made by the Committee on Evaluation of Serodiagnostic Tests for Syphilis appointed by the U. S. Public Health Service. The 1938 evaluation was based on 100 specimens from normal, nonsyphilitic donors, and 207 syphilitic donors. Four tests were performed on each specimen in the bureau of laboratories—the Kline exclusion, standard Kahn, Hinton, and Connecticut complement fixation. When considering specificity Connecticut was among the 23 State laboratories which reported no false reactions with the complement fixation tests. Connecticut obtained specificity ratings of 100 percent with the standard Kahn and the Hinton tests. With the Kline exclusion test, the bureau of laboratories obtained 3 false positive and 7 false doubtful reactions out of 100 tests. Comparing the Connecticut complement fixation test with other complement fixation tests, the bureau of laboratories stood fourth, with a rating of 79.6 percent as to specificity.

With the standard Kahn test it obtained a rating of 75.1 percent, with the Hinton of 82.7 percent, and with the Kline exclusion of 88.8 percent.

The evaluation studies have proved to be of immense benefit to State health department laboratories by furnishing the clinical controls necessary to gain an idea of the efficiency of methods. The Committee on Evaluation has recommended that the States in turn offer such a service to local laboratories, but this will be impossible in Connecticut because of the limited budget under which the bureau of laboratories operates.

Reexamination of cases of early syphilis treated in 1912-1913 (preliminary report). G. Willners (Karolina Institute, Stockholm). *Acta dermat.-venereol.*, Stockholm. Aug. 1939, 20: 463.

Investigation revealed that of 616 patients with early syphilis who were treated at the St. Göran Hospital in 1912-13 about one-fifth of the number had died, three-fifths were still alive (their addresses were known), and one-fifth could not be traced. In the group of those who had died, death had been attributed to syphilis in 11 (1.78 percent), to other diseases in 73 (11.85 percent) and the cause of death was unknown in 32 (5.19 percent) of the total number of cases. In the group of those who were still living there were 19 (3.08 percent), with symptoms of disease. Five of these had symptoms of syphilis, 10 had symptoms of other diseases and 4 had indefinite symptoms. In this group there were also 121 patients (19.64 percent) who were asymptomatic, according to the patient's own statement in 107 and according to the physician's statement in 14 cases. No information could be obtained from the remaining 360 patients. Deaths as a result of syphilitic infection were due to aortitis (3 cases), aortic insufficiency (1 case), hemorrhagic pachymeningitis (1 case), cerebrospinal syphilis (1 case), cerebrospinal thrombosis (1 case), tabes (1 case), and general paresis (3 cases). Except for the death

due to thrombosis which occurred 2 years after infection, the interval between infection and death varied from 8 to 22 years. The important question of the effect of treatment on the disease could not be determined from this material, since treatment at that time consisted mainly of the intermittent use of mercury. The records of the 11 patients who eventually died of their syphilitic infection showed that they had either had no treatment or only an occasional injection for a certain length of time. Among the group of those who had died of diseases other than syphilis, death was caused by pulmonary tuberculosis in 27, the influenza epidemic in 13, by carcinoma in 13, by sepsis and meningitis in 7, by cardiovascular diseases in 7, by gastrointestinal diseases in 4, and by other diseases in 2 of the cases. Among the group of deaths due to uncertain causes there were 3 suicides. A comparison of the death rate among this group of persons with syphilis with that of the general population revealed a 32 percent higher death rate for the syphilitic group. The calculations were made on the assumption that the mortality among the patients who could not be traced was the same as among those who were traced.

LABORATORY RESEARCH

Oxidation-reduction potentials and the mode of action of sulfanilamide. Richard O. Roblin, Jr., and Paul H. Bell. *Science*, New York. Oct. 6, 1939, 90: 327.

The report of Shaffer (*Science*, June 16, 1939) concerning a possible relationship between the potentials developed by certain oxidation products of sulfanilamide and its therapeutic activity contains much that is suggestive. But that the high potentials reported by him are due to oxidation products

of sulfanilamide and are responsible for the activity of the drug is open to question. From their study and experiments, the authors deduced the following facts: (1) In the presence of excess sulfanilamide the potentials fall rapidly as the oxidized form of the oxidizing agent is exhausted. (2) Equilibrium potentials are established if partially oxidized solutions of sulfanilamide are allowed to stand for 48 hours. (3) When an excess of ceric sulfate is present, the equilibrium potentials agree with those calculated for a cerous-ceric system. (4) The "plateau potentials" can be varied within wide limits, depending on the rate of addition of the oxidizing agent.

On the basis of these facts, they believe that the "plateau potentials" of Shaffer are a function of the oxidized and reduced forms of the oxidizing agents employed, rather than of the oxidation products of sulfanilamide.

The mode of action of sulfanilamide.

Arthur Locke and R. R. Mellon. *Science*, New York. Sept. 8, 1939, 90: 231.

In a communication on this subject in the June 16 issue of *Science*, Shaffer suggests the possibility that both the therapeutic and toxic actions of sulfanilamide may be exerted through a "mechanism by which the sterilizing oxidation intensity of molecular oxygen is applied nearly at its maximum to bacteria and unavoidably also to some extent to host cells." Locke and Mellon are in agreement with this conception to the extent that it indicates a source of sulfanilamide toxicity. They do not find the available evidence compatible with a concept of identity between the mechanisms producing the known toxic and those producing the beneficial therapeutic effects, nor with an explanation of the therapeutic usefulness of sulfanilamide in terms of its capacity to act as a reservoir for an intermediate substance of high oxidizing intensity. They discuss their deductions under (1) association of the oxidizing potentialities of the postulated intermediate with the nitroso and not with the hydroxylamine component, (2) insusceptibility of catalase to oxidative injury of the type postu-

lated, (3) successful chemotherapeutic action directed against a type of vulnerability in the pathogen, not shared by the host.

Their alternative suggestion is that, while p-hydroxylamino and p-nitroso benzene sulfonamide are obtainable from sulfanilamide by biologically feasible types of oxidation, they may not be produced together, but rather stepwise. This stepwise production, first of the therapeutically active derivative and, secondly, of the toxic derivative, is possible. It would not be possible as a result of the peroxide-mediated type of oxidation postulated by Shaffer. An assumption of the stepwise production of the therapeutically active and toxic agents opens up the possibility of using, in place of sulfanilamide, an agent making hydroxylamine available in a form not so readily oxidized to a nitrous acid derivative as is p-hydroxylamino benzene sulfonamide.

Adjuvant measures should be taken, during sulfanilamide therapy, to counteract toxic actions on hemoglobin and on circulatory capacity so as to permit full realization of the therapeutic effect.

Experimental and clinical granuloma inguinale. R. B. Greenblatt, R. B. Dienst, E. R. Pund and Richard Torpin. *J. A. M. A.*, Chicago. Sept. 16, 1939, 113: 1109.

The authors have several times obtained pure culture of Donovan bodies in the aspirated pus from unruptured pseudobuboes of granuloma inguinale. They felt that some light might be thrown on the cause of granuloma inguinale if subcutaneous injection of this material could be followed by exact clinical reproduction of the disease as well as recovery of the organism again in pure culture.

Granuloma inguinale was experimentally reproduced in three human beings but failed to develop in one. It failed to develop in laboratory animals in spite of repeated attempts. When the disease was reproduced the course was comparable in every way to that seen in spontaneous cases. Donovan bodies were recovered to the exclusion of other or-

ganisms from the pseudobuboes that developed in each of the three patients. The incubation period could not be determined; however, the disease seemed fully developed in about 50 days. The authors believe this is the first instance in which granuloma inguinale was experimentally produced in a human being by the use of an exudate which contained only the Donovan body and no other demonstrable organisms.

The authors use "pseudobubo" to describe the inguinal swelling which occurs in granuloma inguinale and frequently simulates the bubo of the other venereal diseases. This pseudobubo which so frequently follows a primary focus on the external genitalia is a subcutaneous granuloma. The histopathologic study of the regional and underlying lymph nodes revealed but moderate endothelial hyperplasia. However, Donovan bodies were demonstrated in the underlying cervical and inguinal lymph nodes in two patients, and such observations prove that the Donovan body can and does travel by way of the lymphatics.

The nature of the Donovan body remains an enigma. It is doubtful whether the causal agent of granuloma inguinale has ever been cultivated. Such cultivated organisms on inoculation into human beings have failed in every instance to reproduce the disease. The method of reproduction in mononuclear endothelial cells and the growth requirements of the organism, as well as the clinical behavior of the disease, lead the authors to believe that the Donovan body is a sporozoon.

A simple and time-saving procedure for the identification of *Treponema pallidum*. M. J. Knisely. J. Lab. & Clin. Med., St. Louis. Sept. 1939, 24: 1309.

There has been a tendency in the last few years to supplant the carbon arc dark-field method of identification of *Treponema pallidum* from primary lesions. The necessary equipment is expensive and the preparation laborious and time-consuming. Knisely describes a simple method which has proved very satisfactory and has checked consistently with the dark-field method.

The reagent he uses is a colloidal aqueous solution of silver, sold under the name of collargolum, and it may be purchased in its dilution of 1 part to 20. A drop of the suspected material is placed on a clean glass slide, and an equal amount of the reagent is added. The two are mixed and streaked out by the use of another slide, as slides are prepared for blood differentials. The preparation dries in a few seconds with a metallic sheen and is ready for microscopic examination. Microscopically the unstained *Treponema pallidum* stands out distinctly against a background which ranges from dark yellow to light brown. No attempt should be made to fix the material on the slide and stain subsequently; the resultant preparation will be too thick for examination.

The entire method and identification in most cases can be done in 10 minutes. In addition to simplicity, slides so prepared may be labeled and kept as permanent records.

Blood studies in lymphogranuloma venereum; with special reference to serum proteins. R. H. Kampmeier, D. W. Smith and R. M. Larsen. Am. J. M. Sc., Philadelphia. Oct. 1939, 198: 516.

The authors present the results of blood studies in 67 cases of lymphogranuloma venereum. In 62 cases (92.5 percent) the total amount of serum protein was found to be 8 gm. or more, and the total amount of serum globulin was found to be 3 gm. or more. Derangement of the serum protein occurred at any stage of the disease and apparently persisted permanently. Such changes occurred in patients with buboes, chronic genital lesions, and acute or chronic proctitis, as well as those with rectal strictures.

The change in the proteins was not related to the activity of the lesions, though the globulin level was less often as high in patients with active buboes as in patients with lesions of many years' duration. Possibly this meant that the disease was not established long

enough for the maximum change to have taken place.

The authors offer no explanation of the deranged serum proteins observed. As controls, they made serum protein determinations in a number of cases of chancreoid with buboes and in several cases of secondary syphilis with especially extensive lymphoid involvement, and they found no instances of changes in the protein fractions. Since lymphogranuloma venereum and syphilis occur together in some cases, some of the examples of hyperglobulinemia reported in the past as occurring in patients with syphilis may have been due to coincident lymphogranuloma venereum.

Though the hyperproteinemia due to hyperglobulinemia in cases of lymphogranuloma venereum is not a specific finding, it is a very constant one and is of some diagnostic value. It is a remarkable fact that derangement of proteins persists for many years and is probably a permanent change.

The findings in the 67 cases studied are tabulated in detail.

The in vitro formation of an oxidizing agent by surviving tissues and sulfanilamide. J. S. Harris. J. Clin. Investigation, New York, Sept. 1939, 18: 521.

From the clinical statistics on methemoglobinemia it has been deduced that sulfanilamide is partially converted by the body into some active agent which can function as an oxidant. The author discusses his studies to determine whether the oxidation of hemoglobin is performed by sulfanilamide itself or whether the active agent is produced through the interaction of tissues and sulfanilamide.

Tissues were removed and slices immediately prepared from normal animals which were killed by decapitation. These slices were suspended in Ringer-phosphate solution of pH 7.4 containing glucose, varying concentrations of sulfanilamide, and the saline-washed erythrocytes from normal human blood. The red cells were centrifuged, washed with physiologic saline, hemolyzed with

saponin, and diluted with 1/20 M. phosphate buffer (pH 7.4). Methemoglobin and total hemoglobin were determined spectroscopically. The incubation of erythrocytes with Ringer-phosphate solution containing sulfanilamide never caused the conversion of more than 1 percent of the total hemoglobin to methemoglobin. The incubation of erythrocytes with tissue slices was likewise without appreciable effect on the hemoglobin. However, when liver slices were incubated with sulfanilamide and red cells, the formation of methemoglobin invariably occurred. It was found that methemoglobin was formed whether or not the hemoglobin was contained within red cells, and this suggested that a dialyzable agent was formed through the action of liver or sulfanilamide and that this agent then diffused through the erythrocyte membranes to oxidize the hemoglobin. Experiments were carried out which showed that this conclusion was correct and that the simultaneous presence of tissue and hemoglobin was not necessary.

It is possible that the active agent may owe its effect to an anticalase action. Experiments eliminated the possibility that accumulation of hydrogen peroxide during the metabolism of the red cells might result and might cause the oxidation of hemoglobin to methemoglobin. Using the technic of testing the supernatant fluids (from the incubation of tissue and sulfanilamide) with red cells, it has been found that precipitation of the protein with trichloroacetic acid does not remove the active substance. The agent is dialyzable through ordinary viscose membranes, it is relatively stable at 0° C., and it is destroyed at boiling. The substance can exert its action on red cells when they are suspended in serum.

The formation of an oxidizing agent from sulfanilamide by tissues adequately explains the methemoglobinemia which has been found in patients treated with this drug. It has been suggested by Main, Shinn and Mellon that a substance having an anticalase action is formed by bacteria from sulfanilamide and that the resultant accumulation of hydrogen perox-

ide may explain the therapeutic action of the drug.

The author believes that he has demonstrated that sulfanilamide cannot function as an oxidizing agent on hemoglobin, and that upon the interaction of certain tissues with sulfanilamide an oxidizing agent is formed which can cause the production of methemoglobin.

Attempts to grow *Spirochaeta pallida* on the chorio-allantoid membrane of the living chicken embryo. G. Sterzi and V. Staudacher. *Gior. ital. di dermat. e sif.*, Milano. Aug. 1939, 80: 777.

Attempts were made to grow the Truffi strain of *Spirochaeta pallida* on the chorio-allantoid membrane of the chicken embryo. It was found that the fragments of syphilitic tissue showed little tendency to penetrate the membrane and there was only a slight degree of vascularization. The spirochetes migrated from the fragment in a regular and progressive manner; after 1 hour they could be found at a distance of 1 cm., after 2 hours at about 2 cm., and after 6 hours at 4 cm. The spirochetes contained in the fragment lost their motility at the end of 24 hours but preserved their form, whereas those in the chorio-allantoid membrane showed morphologic changes after 8 to 14 hours. *Spirochaetae pallidae* in these transplants were found to be virulent for a period of 2 hours. Transplants made at the end of 4 hours were negative. Only once could a spirochete be found in the tissues of the embryo and this one was found in the liver. The development of the embryo was not affected by the implant.

PATHOLOGY

Epidemiology, etiology and prophylaxis of lymphopathia venereum. Favre and Sven Hellerström. Reprint from *Rev. d'hyg.*, Paris. June-July 1939.

The authors review the history and literature of this disease since the work of Nicolas and Favre in 1913 and discuss

its epidemiology, etiology, prevention, and treatment on the basis of these reports.

Lymphopathia venereum is now seen in practically all countries and is not necessarily imported from tropical countries as was formerly supposed. Statistics from the different countries are given. Statistics are also given for its frequency in different occupation groups. It is not peculiarly a disease of seamen as was formerly believed.

The primary lesion is of various types, the most frequent being a small erosion of the herpetiform type.

Many pathologic conditions which were formerly thought to be independent diseases are now known to be sequels of lymphopathia venereum. These include esthiomene, stricture of the rectum called by Fournier anorectal syphiloma, and certain forms of vegetating, dysenteroid, and ulcerous anorectitis. Certain forms of orchitis and orchiepididymitis and many polymorphous joint lesions are sequels of lymphopathia venereum. Various skin lesions occur in the course of the disease. In some cases there are neurologic symptoms in the course of which the virus of the disease can be demonstrated in the blood. In some cases there are general symptoms such as asthenia, emaciation, anorexia, and fever.

In 1937 the author sent a questionnaire to 400 dermatovenereologic clinics in different countries. About 10,000 cases of lymphopathia venereum and 1,000 of esthiomene were reported. A similar questionnaire in 1932 revealed only 1,693 cases of lymphopathia venereum and 215 of esthiomene. A table is given showing the results of the 1937 report with regard to distribution by countries, frequency, sex, nature of the disease, clinical forms, association with other venereal diseases, and mortality.

The period of incubation varies greatly in different cases. Periods varying from 3 days to a month have been reported. As a rule the chancre precedes the adenopathy by from 4 to 12 days. Periods as long as 4 months have been reported. The contagious-

ness of the chancre has been demonstrated experimentally. Miyagawa's corpuscles have been demonstrated in chancre. The author does not take a definite stand on the question of whether these corpuscles represent the true virus but says that there is still a great deal of uncertainty in regard to the mode of transmission. In this connection he discusses healthy carriers and the transmission of the disease from genito-anorectal lesions and from esthiomene. There is obviously danger of contamination from chronic genital ulcers.

The primary lesions of paradenitis, like those of syphilis, may be extra-genital.

As to prognosis the inguinal form of adenopathy rarely if ever causes death directly, but the prognosis of the late genital and intestinal forms is serious.

Diagnosis is made by clinical examination and the outcome of the Frei test which is very reliable. It persists indefinitely, however, so that a current lesion may not be due to the lymphopathia venereum. The Frei test may show only an old infection to which some other form of disease is superadded.

Services devoted to the prophylaxis of venereal disease should take into account lymphopathia venereum as well as syphilis and gonorrhea. An educational campaign should be carried on to acquaint the general practitioners with the clinical symptoms of the disease and the methods of diagnosis. There is difficulty however in the fact that there is no definite way of determining the period of contagiousness. The virus may persist for a long time in chronic ulcer and esthiomene. Even without visible symptoms the genital organs of women who have had the disease may be a source of contagion.

In spite of these difficulties the same measures of prophylaxis should be applied as in the other venereal diseases: Sexual abstinence, regular and systematic genital hygiene, and careful cleansing and antisepsis after coitus. Hanschell has noticed that in North Africa the circumcised natives do not contract

the disease while the uncircumcised Europeans do. Formol and glycerine salves have been recommended as prophylactics.

The diagnosis should be made as soon as possible because the inguinal adenopathy is the form of the disease most amenable to treatment. Even incomplete removal of the diseased glands by a skillful surgeon shortens the course of the disease. Physiotherapy and radiotherapy have been used with good results.

The genital and anorectal lesions are harder to treat. Women with such lesions should be warned that their disease is contagious and that it may be transmitted to their children. Prostitutes with chronic vulvovaginal ulcer should be hospitalized until they are completely cured.

Practitioners, surgeons, hygienists, venereologists, and public health officers should unite in the effort to overcome this disease. Specialists in diseases of the digestive tract, especially the large intestine, in gynecology, and in venereology should be on the look-out for it and should help in making an early diagnosis.

As much information on this new venereal disease as possible should be collected particularly in regard to epidemiology and modes of contagion in order to help in prevention and early detection.

Contact ulcers in granuloma inguinale.

Richard Torpin, Everett S. Sanderson and Robert Brandt. *Urol. & Cutan. Rev.*, St. Louis. Sept. 1939, 43: 617.

Nothing is known about the immunologic factors of granuloma inguinale. Animals are not susceptible to inoculation, and experiments on man must not be performed on a broader scale as long as no reliable remedy is available. The authors feel, therefore, that the cases they are reporting are of value in adding clinical observations although the conclusions may be merely preliminary.

A Negro woman had a bleeding ulcer in the vaginal introitus on the left side, and two weeks later a similar ulceration

developed in the right side opposing the original ulcer. Another Negro woman had a large ulceration in the right upper vaginal wall, and directly opposite in the left wall was a small early ulcer. Later a Negro man was seen who had typical granuloma inguinale lesions in the inguinal region and multiple lesions over the scrotum. In several places on the inner aspects of the thighs there were typical elevated rolled-edge ulcers facing those on the scrotum with which they were in contact.

In diseases of a chronic character usually a state of immunity develops which is not sufficient to kill the germs or prevent them from spreading slowly within the tissue, but it does prevent the patient from acquiring a superimposed infection from within or without. The occurrence of contact infection, as demonstrated by these reported cases, suggests that a low degree of local immunity is present in granuloma inguinale. If the wide open surface of the lesion, the frequently large number of Donovan bodies in the tissues, the long duration of the disease, and the lax sexual habits are considered the incidence of granuloma inguinale seems strikingly small. This can possibly be attributed to a low penetrating power of the infecting agent.

Infectious relapse in syphilis of more than two years' duration. Harry Pariser. J. A. M. A., Chicago. Sept. 23, 1939, 113: 1206.

Although infectious relapse in syphilis is largely a problem of the first 2 years of infection, a significant number of cases relapse after this period. During the course of examination of 120 patients at the syphilis clinic of the hospital of the University of Pennsylvania whose infection was 2½ years or more in duration, 6 were found to have suffered an infectious relapse. Five of the 6 patients had been given more than the "adequate" treatment, namely, 20 injections of an arsenical and a corresponding number of heavy metal treatments; 3 of the 5 received this treatment irregularly. Two of the patients in whom

relapse occurred began treatment in the seropositive primary stage. Four showed a tendency toward early serologic reversal.

The authors say that their purpose in recording this group is to emphasize the fact that infectious relapse can occur for many years after the original infection and to stress that numerically "adequate" treatment does not insure non-infectiousness, especially when given irregularly. No rule is infallible as to the total amount of treatment or the time that must elapse to render the individual patient continuously noninfectious. When possible, it is wiser to strive for the Cooperative Clinical Group standard of from 30 to 40 arsenical and 60 weekly bismuth injections than for the artificial median of 20 arsenical and 20 bismuth injections employed as a device for statistical evaluation.

Aneurysm of the vertebral artery.

Peter Bassoe. Arch. Neurol & Psychiat., Chicago. July 1939, 42: 127.

Two cases of aneurysm of the vertebral artery are reported and the literature on the subject is reviewed.

In one case the patient's history over a period of 23 years and the post-mortem findings are given. The important pathologic findings in this patient were saccular aneurysm in the region of the pons and bulb, syphilitic aortitis, atrophy of the cerebral cortex, unresolved bronchopneumonia, acute suppurative frontal sinusitis, emaciation, dehydration, generalized arteriosclerosis, and atrophy of the right leg. In the ascending portion of the aorta were 3 large, calcified plaques, one 15 by 9 mm. and the other 15 by 8 mm. In the anterior portion of the brain there was considerable cortical atrophy, wide sulci, and an increased amount of subarachnoid fluid. Photographs are presented of the aorta, a cross-section of the brain showing the aneurysm of the left vertebral artery, and the base of the brain showing two aneurysms of the basilar artery and the aneurysm of the left vertebral artery.

The second patient did not have syphilis.

There is some difference of opinion regarding the frequency of cases in which syphilis has caused aneurysms of the vertebral artery. Considerable search of the literature has led the author to believe that syphilis rarely produces the rather common small aneurysms on the circle of Willis, but that it is more often a cause of the less frequent large aneurysms of the basilar and vertebral arteries.

Syphilitic polyneuritis. A clinicopathologic entity. Alexander Simon and Sidney Berman. *Arch. Neurol. & Psychiat.*, Chicago. Aug. 1939, 42: 273.

In spite of the great frequency of syphilis of the central nervous system, it is rare that the peripheral nerves are involved in syphilis. Occasional cases of syphilitic polyneuritis have been reported in all stages of the disease. The clinical signs are the same as those in polyneuritis of nonsyphilitic origin. Sharp, lancinating, boring pains along the course of the nerve, tenderness on pressure over the nerve trunk or muscle, motor weakness and paralysis, areas of loss of sensation, loss of deep reflexes, and muscular atrophy may occur. Depending on the nerves involved, the syndrome may be purely motor or purely sensory, or may have mixed motor and sensory signs. The Wassermann reaction of the blood is usually positive and that of the spinal fluid may or may not be positive. The fundamental pathologic process is panvasculitis with lymphocytic and plasma cell infiltration in and about the walls of the blood vessels, associated with intimal proliferation, leading to obliterative endarteritis and endophlebitis. This pathologic process is spread by the circulation and may occur in any body organ, with the clinical picture of peripheral neuritis resulting from its localization in the peripheral nerves. The prognosis in most cases is favorable if early, regular, and sufficient anti-syphilitic therapy is given.

One case is reported in detail, including the findings of the neurologic and post-mortem examinations. Five photomicrographs are presented which clearly

illustrate the pathologic changes in the blood vessels and nerves.

Intracranial aneurysms. Charles A. McDonald and Milton Korb. *Arch. Neurol. & Psychiat.*, Chicago. Aug. 1939, 42: 298.

The authors have reviewed 407 articles on this subject which appeared from 1761 through 1937, and they have collected 1,125 cases of saccular aneurysm of the arteries at the base of the brain verified at autopsy or operation. From these cases they constructed a reference bibliography. The articles are tabulated chronologically according to the year of their publication. The cases are numbered, and for each case the table gives the artery involved, the age and sex of the patient, whether the aneurysm had ruptured, the appearance of the arteries at the base of the brain, the author of the article, and the reference.

The appearance of the arteries at the base of the brain was described in 572 cases. In 385 (67.3 percent of the 572 cases) the vessels had pathologic changes. In 32 (5.6 percent) these pathologic changes were caused by syphilis. The ages of these 32 patients ranged from 20 to 75 years.

The authors add to the literature the report of 2 cases. In one of these patients there was an anomaly of the circle of Willis with a ruptured aneurysm, extensive arteriosclerosis, and syphilitic aortitis. The patient was only 24 years of age when he died. At the age of 17 he had had left hemiplegia and possibly an area of softening in the right internal capsule. The post-mortem findings are reported. In the second case, there were no signs of syphilis.

The causes of dizziness. Kemp G. Cooper. *Rocky Mountain M. J.*, Denver. Oct. 1939, 36: 703.

Among the important causes of dizziness the author lists syphilis. The pathologic changes due to syphilis are gradual and the dizziness is mild and variable. It is usually accompanied by

marked tinnitus and a nerve type of deafness. The pathologic changes include degeneration of nerve endings and auditory nuclei (or the neurologic connections). In obscure cases a positive Wassermann test of the spinal fluid is of considerable diagnostic value.

DIAGNOSIS

Interpreting syphilis tests. Physicians Bull. (New Jersey State Department of Health), Trenton. Sept. 1939, 1: 3.

The following interpretation applies to a complement fixation or flocculation technic having approximately the same sensitivity as a technic which produces a (just) positive report on a serum that is plus 2 to a diagnostic Kline, plus 4 to the exclusion Kline, and 024 (plus 2) to the Kahn test.

Repeat every test once, (1) when negative, if an apparent primary lesion or other suspicious sign is present; (2) when doubtful; (3) when positive in the absence of definite clinical evidence. A negative report almost excludes syphilis if no treatment has been given and if primary syphilis is not present. A doubtful report is most common in treated cases of syphilis and occurs sometimes in malaria, high fever, pregnancy, in some severe metabolic disturbances, and in some healthy persons. A positive report usually indicates the presence of syphilis; but it also occurs in 50 percent of cases of leprosy and rarely in malaria, high fever, and other severe metabolic disturbances. If a test is positive on two consecutive specimens of blood in an apparently healthy person, a diagnosis of syphilis is indicated. Qualitative tests on infants under 4 weeks of age are not conclusive. Negative tests in the presence of old, untreated syphilis are less common in persons under 30 than in older persons. In persons over 30, the chances of a negative test (in a good laboratory) in the presence of syphilis are somewhat more

than 5 percent. In such cases, the spinal fluid should be tested for syphilis.

Serologic tests made on blood specimens obtained from the umbilical cord are not considered reliable for determining the presence of syphilis in newborn children. The syphilitic antibody from the mother may be present in the specimen when the child is not infected. Neither does a negative cord serologic test always exclude the presence of syphilis in the child. A test of the child is best made at the age of 1 month, and, if positive, it should be repeated in 1 week. If negative, another test should be made 1 month later to exclude syphilis. One cc. of blood taken from the big toe is a sufficient quantity to permit performance of flocculation tests.

Methods for the examination of spinal fluid. Carl Lange. Am. J. Syph., Gonorr. & Ven. Dis., St. Louis. Sept. 1939, 23: 638.

Standardization of the diagnostic examination of spinal fluid lags spectacularly behind other laboratory determinations and every one of its points is still controversial. The standardization of technic is only one factor in the examination of spinal fluids. In addition, it is important to consider the standardization of collection, transportation, preservation, selection of the various examinations based upon their value in the diagnosis of various diseases, and interpretation of results.

The author discusses in detail (1) collection, transportation, and preservation of spinal fluid, and (2) general selection of examinations and interpretation of findings. Under the second topic, the following subjects are discussed: (1) General course of examination as determined by the appearance, (2) general survey of nonbacteriologic methods and their specific or etiologic significance, (3) technic of the selected nonbacteriologic tests. The technic, errors, and interpretation of results and correlation with other tests of quantitative and qualitative cell determinations are described. The protein examinations described are (1) quantitative protein

examination bearing on the determination of total protein, (2) qualitative protein examinations bearing on the percentage mixture of protein fractions, and (3) quantitative and qualitative protein examination combined in the gold reaction. Serologic examinations and quantitative chemical determination of permeability (sugar determination of Hagedorn-Jensen and the chloride determination in blood and spinal fluid) are also described.

For interpretation of tests it is first necessary to know whether the fluid was collected by lumbar, cisternal, or ventricular puncture because fluids from these three loci have perceptibly different constitutions. It is necessary, also, to know how much fluid was collected because by a large drainage the different portions may be mixed. Lumbar puncture is the method of choice in cases of syphilis.

Contaminants may be bacteria, dirt, or blood. Speed in collection, secured by sufficient training and avoiding unnecessary procedures, is the most important factor in avoiding bacterial contamination. The potentially deleterious effect of even slight blood contamination upon every kind of spinal fluid examination has been strongly underrated, as demonstrated by an appallingly high percentage of blood-contaminated specimens received by a central laboratory. The importance of avoiding blood contamination is appreciated if it is remembered that blood plasma contains 300 times more protein than normal spinal fluid; that whole blood contains 6,000 times more white cells; that a syphilitic blood serum may yield marked complement fixation reaction in dilutions up to 1:1,000; and that, in bacteremia, blood not only may contaminate the fluid collected for examination but may infect the previously sterile subarachnoid fluid. For the evaluation of the findings in the spinal fluid, it is necessary to submit a simultaneously collected blood specimen and to communicate the pertinent clinical data.

A positive Wassermann reaction in the spinal fluid may induce erroneous conclusions regarding both its etiologic and

local significance since blood reagins may get into the spinal fluid either spontaneously (by increased permeability) or artificially (by bloody tap). Accordingly, there are several possibilities for misleading results in the complement fixation reaction, but it has undoubtedly a higher degree of etiologic significance (specificity) than the gold reaction. The gold reaction provides 3 different results: (1) The exclusion diagnosis, (2) the detection of the slightest degree of syphilitic inflammation, (3) the discrimination of paresis. The paretic curve is in its significant part as nonspecific as the exclusion diagnosis because it is elicited by the admixture of products of secondary parenchymatous destruction with the products of syphilitic inflammation.

The clinical application of a twenty-minute staining method for *Spirochaeta pallida* in tissue sections.
Aram A. Krajian. *Am. J. Syph., Gonorr. & Ven. Dis.*, St. Louis. Sept. 1939, 23: 617.

The author presents a 20-minute staining method for biopsy material containing *Spirochaeta pallida*, as follows: (1) Boil 10 percent formaldehyde, drop a small piece of biopsy material into it, and agitate for 1 minute (formol-fixed tissues do not require this); (2) cut frozen sections 7 to 10 microns; (3) place sections in No. 1 solution (uranium nitrate, 1 gm.; 85 percent formic acid, 3 cc.; glycerine, 5 cc.; acetone, 10 cc.; 95 percent alcohol, 10 cc.); (4) rinse in distilled water; (5) treat for 5 seconds in a dilute gum mastic solution prepared by mixing well 3 drops of saturated alcoholic solution of gum mastic in 5 cc. of 95 percent alcohol; (6) rinse and spread out section in distilled water; (7) place in a wide-mouth pyrex beaker containing 30 cc. of 1 percent silver nitrate solution (under electric light); (8) heat the silver solution until bubbles form, keep temperature at 70° C. to 73° C. for 7 minutes; (9) without washing, carry individual sections with glass rod lifter to warm developing solution (hydroquinone, 0.31 gm.; sodium sulfite, 0.10 gm.; 40 percent solution of formaldehyde, 2.5 cc.; acetone,

2.5 cc.; pyridine, 2.5 cc.; saturated alcoholic solution of gum mastic, 2.5 cc.; distilled water, 15.0 cc.), alternately dipping into the solution and then exposing all portions of the section on the lifter to a strong electric light, repeating the process 6 to 8 times or until section assumes a strong brown color; (10) wash section for a few seconds in 95 percent alcohol; (11) rinse section in distilled water and spread it out by surface tension—if it is folded over, continue treatment with alcohol further until completely smooth; (12) again place section in silver solution for 10 to 20 seconds and rinse in distilled water; (13) place section in a large basin of tap water and transfer to a glass slide; (14) blot with fine filter paper; (15) dehydrate for 30 seconds with absolute alcohol or anhydrous isopropanol; (16) blot twice with filter paper and dip in thin celluloidin once; (17) place in neutral xylene for 1 minute, blot twice and place in xylene for a few seconds; (18) mount in gum damar.

Biological and chemical studies of the serological tests used in the diagnosis of syphilis. Noble P. Sherwood, Glenn C. Bond and Harold F. Clark. (Proc. Missouri Valley Branch, Soc. Am. Bact.) J. Bact., Baltimore. Aug. 1939, 38: 231.

The objectives of this investigation were: (1) A study of the distribution of "reagin-like" substances in the blood of beef, sheep, horses, rabbits, guinea pigs, dogs, hogs, chickens, and snakes by means of routine Kolmer-Wassermann, Kahn, Kline, and a "widespread modification of the Kahn" technics. In the latter test standard Kahn antigen was used and ratios of serum to antigen varying from 100:1 to 0.19:1 were employed. The ratios used in the 3-tube Kahns were included in the series. Positive serologic findings were obtained quite frequently with all species studied except the guinea pig. The Kolmer was less frequently positive than the flocculation tests. (2) Using Howe's method of fractioning beef and horse serum it was ascertained that the "reagin-like" substance was present

in either or both the euglobulin and pseudoglobulin I fractions and it was destroyed at about the same temperature as syphilitic reagin. (3) When various animal serums and serums from untreated and treated cases of syphilis were studied by means of the special flocculation technic to determine optimum ratios or zones of flocculation, certain rather striking results were obtained: (a) in untreated cases of secondary syphilis where the reagin titer is high the optimum zone of flocculation was frequently between 20:1 and 0.25:1. In treated cases there was a definite shift toward the higher ratios and a narrowing of the zone. A few clinically cured ones were negative in all ratios while others that were negative in the diagnostic ratios gave strong flocculation in higher ratios, i. e., 12:1. (b) The zones of flocculation observed with animal serums resembled the ratios in many treated cases. This indicates a low titer of the "reagin-like" substance.

An evaluation of the Laughlen test in the diagnosis of syphilis. A report based on 2,005 tests. J. Churg and N. Sobel. New York State J. Med., Albany. Sept. 15, 1939, 39: 1754.

The authors made this study under conditions comparable to those in a doctor's office or in a small laboratory. The patients were those attending the Central Social Hygiene Clinic, New York City. With slight modification the directions given by the manufacturer of the antigen were followed. The 2,000 Laughlen tests were compared with the routine Wassermann tests done on the same specimens by the serologic laboratory of the city of New York.

In the series of 356 tests done according to the original directions, with unheated serums, there was agreement in 72 percent. The addition of larger amounts of saline solution to the antigen and the heating of the serums gave varying results. In the 193 tests with heated serums and 0.25 cc. 10 percent NaCl to 1 cc. of antigen there was agreement in the two tests in 82 percent of the tests. Technical skill is required, and not until 300 tests had

been performed were the authors sure of their results. The authors believe that until the conditions of its proper performance are determined the Laughlin test cannot be recommended for routine use, nor can it be recommended for use by physicians and other persons without special training in serology.

A quick and reliable method for staining gonococcus smears. Seth T. Walton. *J. Lab. & Clin. Med.*, St. Louis. Sept. 1939, 24: 1308.

Walton describes the technic which he has used for 3 years in staining gonococcus smears. By its use there is often found a single organism, or a single pair, or several single gonococci which are easy to see with the deep-contrasting stain, but which are extracellular and not typically grouped. They do not resemble the gonococcus enough to warrant a positive report, but the finding is sufficiently important to warrant further search; eventually, a typical nest of gonococci can be found. This stain is not selective for the gonococcus but for the Neisserian group of micro-organisms.

The method is a modification of the Pappenheim-Saathof formula found in Conn's book, *Biological Stains*, 1929. The main variation is the substitution of 10.0 cc. of absolute methyl alcohol for the 5.0 cc. of 95 percent ethyl alcohol, which appears to make a great difference in the stability of the staining solution. Gonococci take the pyronine readily and stain a deep red color. All other bacteria are stained a pale purplish color and are barely noticeable. The nuclei of pus cells are green and the cytoplasm is a soft pink or rose color.

The time interval in reading the Kahn test. Elizabeth C. Brown and Nathan Nagle. *J. Lab. & Clin. Med.*, St. Louis. Sept. 1939, 24: 1301.

Several known factors which influence the Kahn test, viz., sensitivity of antigen, time and temperature of heating serums, and shaking time and speed have been standardized. The authors have recently

observed that the time interval in reading the Kahn test after the addition of physiologic salt solution following the shaking period definitely influences the sensitivity of the test. Accordingly, 1,500 routine Kahn tests were read at the following three intervals: Immediately, 10 minutes, and 20 minutes after the addition of the salt solution. Of the 1,500 tests made, 481 serums gave positive or doubtful results when read at any of these intervals, while 1,019 tests were negative. The results of the study indicate that 18.1 percent of the readings changed during the 10 minutes after the salt solution was added, while 22.7 percent changed during the 20-minute interval. Of the 18.1 percent readings that changed within 10 minutes, 3.4 percent became stronger, and 3.8 percent of the 22.7 percent that showed changes during the 20-minute period also became stronger. It is important that 22 (5.1 percent) of 433 final "positive" reports changed to final "doubtful," and 2 changed to final "negative" reports when read 10 minutes after the addition of the salt solution. Furthermore, 18 (4.1 percent) changed from final "doubtful" to "negative" reports when read after 20 minutes.

The authors, therefore, believe that before comparable results can be obtained with the Kahn test in two or more laboratories, even though the standard technic is followed and the same lot of antigen is used, it is necessary to standardize the time factor in reading the test. If the test is read immediately a larger number of "positive" reactions will be found than if the test is read 10 or 20 minutes after the addition of the salt solution.

TREATMENT

General paralysis of the insane in Victoria. F. G. Prendergast. *M. J. Australia*, Sydney. Sept. 2, 1939, 2: 361.

Annual reports of the Victoria Department of Mental Hygiene show that the present incidence of general paralysis of the insane is much lower than it

was 25 to 30 years ago, but Prendergast feels that these figures need correction, due to several factors, such as the admission of voluntary boarders to the mental hospitals and the more general use of the Wassermann test. He believes that the "corrected" figures indicate that there has been no substantial decline in the number of admissions over the last 20 years. In regard to the future, if the present reported decline in primary syphilis is taking place, then there should be a corresponding drop in the incidence of general paralysis of the insane, but that cannot be expected to take place for 15 to 20 years more. It is now almost 30 years since salvarsan was introduced, and yet there are still enough cases of general paralysis of the insane to cause concern.

In order to study the effectiveness of treatment, the results were checked in a series of 66 consecutive male patients admitted to Mont Park (1936-38). All of the patients, except one, were treated with malaria combined with one or more courses of tryparsamide. The percentage of remissions was found to be 13.5; of improved cases, 21.0; arrested cases, 36.0; progressive cases, 16.5; and deaths, 12.0. Prendergast feels these figures give no cause for complacent belief that modern therapy is coping effectively with general paralysis of the insane.

Study of reliable histories in 52 of these 66 cases shows that 28 patients had a history of overt symptoms of general paralysis for longer than 6 months. The author feels that it is to this 50 percent of cases that attention must be directed if improvement in the results of therapy is to be hoped for. In these 28 cases, 17 had been under medical observation for at least 6 months prior to admission. The importance of the two syndromes noticed most frequently in 8 undiagnosed cases is emphasized—first, the onset of epileptic seizures in middle-aged men, and second, a slow onset of mental enfeeblement and dulling of cerebration. In a further 7 cases the patients were under antisypilitic treatment for 2 or 3 years, but no examinations of the cerebro-

spinal fluid had been made. The fluid of early syphilitics should be examined after 6 months' intensive treatment or before discharge as "cured," for only in this way can it be determined which patients are actually neurosyphilitic. Prendergast believes that a patient whose fluid yields a strongly positive Wassermann reaction, an increased protein and cell estimation, and a gold curve of the parietic type should be immediately given a course of fever therapy although there may be no clinical symptoms of general paralysis of the insane.

The importance of early treatment is shown by the fact that, whereas only 30 percent of the patients in the late stages improved, 55 percent of those in the early stages did so. There should be greater education of the public and of physicians as to the need for early diagnosis and treatment. Unless every aid is made use of, general paralysis of the insane will continue to take its steady toll of human life.

The prognosis of treated syphilis. E. Lomholt. *Acta dermat.-venereol.*, Stockholm. Aug. 1939, 20: 482.

The author discusses the prognosis of syphilis in regard to the development of late involvement of the central nervous system. He stresses the frequently emphasized point that spinal puncture ought to be looked upon as an indispensable part of the examination of an otherwise symptom-free syphilitic. To be sure that the effect of antisypilitic treatment is permanent, he advises that spinal puncture be made not immediately after the conclusion of treatment but that it should be delayed for 1 year. His experiences at the Rigshospital warrant the statement that in all probability neurosyphilis will not develop if the patient is symptom-free and has a normal spinal fluid 1 year after antisypilitic treatment has been stopped. A survey of the world literature revealed only one exception to this rule. This was a case reported by Meyerbach in which general paresis developed in a patient with latent syphilis who had a normal spinal fluid during

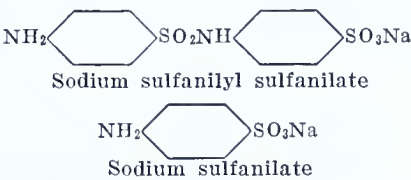
atency. The author urges that similar cases, if they have been observed, should be reported in detail, in order to throw more light on the question of the prognosis of syphilis.

A brief survey is given of the results of an examination of the histories of 538 male patients with syphilis who were treated for early syphilis at the Rigshospital in the period from 1911 to 1920. Of this number 217 were treated in the primary stage of syphilis and in 3 of them general paresis subsequently developed; 321 were treated in the secondary stage and in 15 of them general paresis later developed. The author concludes: "So this material furnishes no evidence in support of the assertion that patients treated abortively would be more liable to get paralysis than are secondary syphilitics." The period of observation varied between 14 and 23 years. The morbidity from general paresis was calculated to be 90 per 1,000, or approximately 9 percent, taking into consideration that it may have its onset from 5 to 35 years after the infection. The author states that it is possible that the more intensive antisyphilitic treatment which has been given since 1920 will lower the morbidity from general paresis.

The treatment of lymphopathia venereum with sodium sulfanilyl sulfanilate and sodium sulfanilate. By Arthur Hebb, S. G. Sullivan and Lloyd D. Felton. Pub. Health Rep., Washington. Sept. 29, 1939, 54: 1750.

During the last 30 years Hebb has been treating the tertiary stage of lymphopathia venereum with many different therapeutic measures. Colostomy, while only a temporary measure, was the only treatment which afforded relief to the patient. The report of Dochez and Slanetz on the antiviral activity of sodium sulfanilyl sulfanilate in dog distemper led the authors to try this drug in the tertiary stage of lymphopathia venereum. In addition to this compound, a simpler one was also studied, the sodium salt of sulfanilic acid, so-

dium sulfanilate. The structural formulas of these compounds are:



Fourteen cases of lymphopathia venereum, diagnosed by positive Frei tests, with demonstration of rectal stricture and high globulinemia, were cured or greatly improved by prolonged treatment of 6 to 35 weeks with either or both of the above compounds. There was a cessation of the bloody purulent discharge, disappearance of fistulas, and absorption of the rectal stricture. Four of the cases, in which colostomy had previously been performed with no improvement, responded to treatment with closure and healing of colostomy and restoration of normal bowel function.

The number of cases reported is small, but the beneficial and curative action of these agents in the chronic tertiary stage of lymphopathia venereum would seem to make the result significant. Most of these patients have been under observation for over a year, and there can be no question that the majority have been cured, judging by the disappearance of the rectal stricture and improvement in general health. The Frei test, however, is still positive and recurrence is possible. Accordingly, patients should be followed over a period of years and treatment repeated if necessary.

The intravenous injection was used throughout in these reported cases. However, other cases have been treated by mouth with sodium sulfanilate and their results indicate that oral administration would be at least as effective as intravenous injection and, perhaps, the method of choice. Sodium sulfanilate is almost tasteless, but sodium sulfanilyl sulfanilate is somewhat disagreeable to the taste.

The reactions were similar to those with sulfanilamide but not so severe. With the doses used, blood hemoglobin content was not decreased, but increased. With sodium sulfanilyl sulfanilate the number

of white cells was not reduced; with sodium sulfanilate, although the leukocyte count was somewhat reduced after prolonged treatment, there was no evidence of bone marrow degeneration.

The authors say that no conclusions as to the relative merits of the two drugs may be drawn from this preliminary paper. Much must be learned as to the optimum blood concentration as well as the route and mode of medication. An effective blood level concentration was found to be 2.5 mg. percent for oral administration of sodium sulfanilate. The authors emphasize that, whatever the method of medication, blood studies must be made at frequent intervals.

If these observations are substantiated by successful treatment of a significantly large number of patients in the tertiary stage of lymphopathia venereum, then the use of a chemotherapeutic agent as a cure for the chronic state of a virus disease would be established. Sulfanilamide has already been successfully used in the earlier stages of this disease, and a program making use of sulfanilamide, sodium sulfanilate, or sodium sulfanilyl sulfanilate would readily determine whether these compounds kill the virus.

Histories are given for the cases considered.

Massive dose chemotherapy of early syphilis by the intravenous drip method. Harold Thomas Hyman, Louis Chargin, John L. Riee and William Leifer. J. A. M. A., Chicago. Sept. 23, 1939, 113: 1208.

In his introduction, Rice says that the experiments of Chargin, Leifer and Hyman in 1933 with a new technic for introducing large amounts of fluids and drugs by means of the intravenous drip seemed to open a new vista to syphilis control measures. Twenty-five patients with recently acquired syphilis were given massive dose chemotherapy with the intravenous drip, and at the end of 5 years a check-up showed that very satisfactory results had been obtained. A committee for further study of this

problem was appointed by Rice, and the results of their work in a group of 86 patients are published herewith.

The massive dose method of chemotherapy in early syphilis apparently yields immediate clinical and serologic results that equal the best results that are obtainable by the optimal methods of routine continuous treatment. The febrile reactions, the toxicodermas, the neuritides, and particularly a fatal incident due to hemorrhagic encephalitis cause the authors to emphasize that this method of treatment must still be considered in an experimental phase and should not be employed for routine clinical use until greater safeguards have been established. Vitamin therapy, both for prophylactic and for curative purposes, has proved ineffectual in the management of the toxic phenomena. The authors are not yet satisfied, however, that the factor of toxicity cannot be greatly reduced.

Massive dose chemotherapy, if it proves safe, practicable and effective, holds out the possibility of greater convenience, a greatly shortened period of infectivity, removal of the syphilitic person from circulation during his active months, and a course of therapy to be measured in days rather than months. It is too soon to judge the ultimate effect of the method, though the small group of cases followed for a period of 5 years appear to be clinically and serologically cured.

Discussion: Vonderlehr says that any new method or drug advocated must meet the following requirements before it can be accepted as an equal of the continuous-alternating scheme of treatment described by the Cooperative Clinical Group: (1) The new method must be as actively spirocheticidal as the continuous-alternating method and must heal open lesions as quickly. (2) It must prevent the communicable forms of relapse with the same degree of efficiency. (3) It must prevent the late crippling manifestations of syphilis to the same extent. The toxic reactions with the two schemes must also be considered.

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